DATE 6-13-07 APPLICATION NUMBER 10/071358

DOC CODE TERM-REQ DOC DATE 5-3-07

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10/071358

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 6,713,485

Issued: March 30, 2004

Inventors: Malcolm Clive Carter, George Stuart Cockerill, Stephen Barry Guntrip, Karen Elizabeth Lackey, Kathryn Jane Smith

Assignee: SmithKline Beecham Corp.

For: HETEROCYCLIC COMPOUNDS

I hereby certify that the following correspondence:

Cover letter for PTE
Application for PTE
Declaration for PTE
Exhibits for PTE

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on May 3, 2007.

Allyson K. Jacobs

Allyson K. Jacobs

EV330918735US

(Express Mail Label Number)

#11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 6,713,485

Issued: March 30, 2004

Inventors: Malcolm Clive Carter, George Stuart Cockerill, Stephen Barry Guntrip, Karen Elizabeth Lackey, Kathryn Jane Smith

Assignee: SmithKline Beecham Corp.

For: HETEROCYCLIC COMPOUNDS

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

Sir:

Applicant, SmithKline Beecham Corporation (DBA GlaxoSmithKline), a corporation of the State of Pennsylvania, represents, pursuant to 35 U.S.C. § 156(d)(1), that SmithKline Beecham Corporation is the record owner and assignee of the entire right title and interest in and to: Letters Patent of the United States of America No. 6,713,485; granted on March 30, 2004 for HETEROCYCLIC COMPOUNDS by virtue of assignment of the parent application 09/582,746 (now U.S. Patent No. 6,727,256) to Glaxo Wellcome, Inc., subsequent corporate merger between Glaxo Wellcome, Inc. and SmithKline Beecham Corporation, followed by an assignment of the instant patent to SmithKline Beecham (Cork) Ltd., and an assignment to SmithKline Beecham Corp. Copies of these documents are provided in the following exhibits:

EXHIBIT 1A is a copy of the assignment from inventor Karen Elizabeth Lackey to Glaxo Wellcome Inc., which was recorded against U.S. Patent Application No. 09/582,746 in the United States Patent and Trademark Office on March 1, 1999, Reel 009804, Frame 0668.

EXHIBIT 1B is a copy of the assignment from inventors Malcom Clive Carter, Geroge Stuart Cockerill, Stephen Barry Guntrip, and Kathryn Jane Smith to Glaxo Wellcome Inc., which was recorded against U.S. Patent Application No. 09/582,746 in the United States Patent and Trademark Office on November 14, 2000, Reel 011281, Frame 0024.

EXHIBIT 2 is a copy of the Articles of Merger, which was recorded against U.S. Patent Application No. 10/071,358 in the United States Patent and Trademark Office on May 2, 2005 on Reel 016500, Frame 0822.

EXHIBIT 3 is a copy of the assignment from SmithKline Beecham Corporation to SmithKline Beecham (Cork) Limited, which was recorded against U.S. Patent Application No. 10/071,358 in the United States Patent and Trademark Office on August 29, 2006, Reel 18184, frame 0080.

EXHIBIT 4 is a copy of the assignment from SmithKline Beecham (Cork) limited to SmithKline Beecham Corporation, which was recorded against U.S. Patent Application No. 10/071,358 in the United States Patent and Trademark Office on December 20, 2006, frame 018654, frame 0335.

Applicant further represents, pursuant to 37 C.F.R. § 1.785(d), that Applicant is the holder of the regulatory approval granted by the Food and Drug Administration ("FDA") for TYKERB® Tablets. A copy of the Food and Drug Administration (FDA) Approval Letter for TYKERB® Tablets is attached as **EXHIBIT 5**.

Applicant hereby submits this Application for Extension of Patent Term under 35 U.S.C. § 156 by providing the following information pursuant to 37 C.F.R. § 1.740. For convenience, the information contained in this application will be presented according to the format set forth in 37 C.F.R. § 1.740(a).

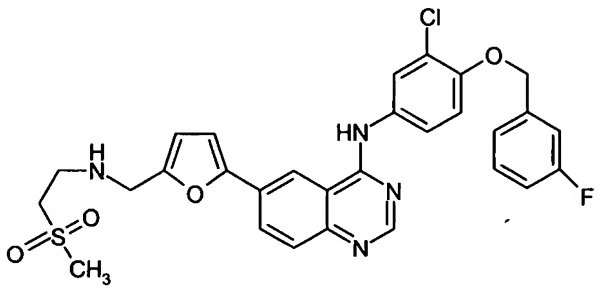
(1) This application for patent term extension is based upon the regulatory review period before the FDA, of Applicant's approved product, TYKERB® Tablets. The only active ingredient in TYKERB® Tablets is lapatinib. A copy of the package insert approved by the FDA as part of New Drug Application (NDA) 22-059 is attached hereto as **EXHIBIT 6**. Identification of lapatinib is provided as follows:

Chemical name: *N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine

Molecular formula: $C_{29}H_{26}ClFN_4O_4S$

Molecular weight: 581.1

Structural Formula:



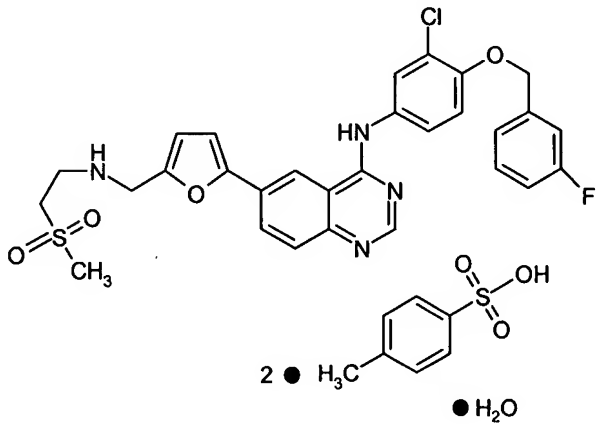
Lapatinib is present in the approved product as the monohydrate of the ditosylate salt. Identification of lapatinib ditosylate monohydrate is provided as follows:

Chemical name: *N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-methylbenzenesulfonate) monohydrate

Molecular formula: $C_{29}H_{26}ClFN_4O_4S\ (C_7H_8O_3S)_2\ H_2O$

Molecular weight: 943.5.

Structural Formula:



(2) The approved product, TYKERB® Tablets was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, section 505 (21 U.S.C. § 355). See **EXHIBIT 5**.

(3) TYKERB® Tablets received permission for commercial marketing and use under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) on March 13, 2007. See **EXHIBIT 5**.

(4) Lapatinib, the only active ingredient in TYKERB® Tablets, has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60-day period, which will expire on May 12, 2007.

(6) The complete identification of the patent for which extension of term is being sought is as follows:

U.S. Pat. No.: 6,713,485

Inventors: Malcolm Clive Carter, George Stuart Cockerill, Stephen Barry Guntrip, Karen Elizabeth Lackey, Kathryn Jane Smith

Assignee: SmithKline Beecham Corporation

For: HETEROCYCLIC COMPOUNDS

Issued: March 30, 2004

Expiration Date: January 8, 2019

(7) A complete copy of the patent identified in paragraph (6) above is attached hereto as **EXHIBIT 7**.

(8) Regarding U.S. Pat. No. 6,713,485:

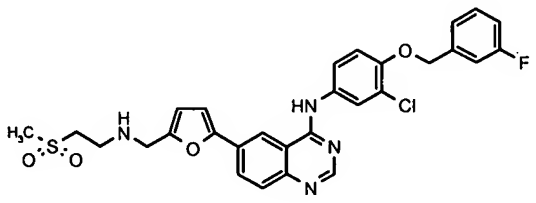
(a) No maintenance fees have been paid for this case. The first maintenance fee payment is due by March 31, 2008

(b) No reexamination certificate exists in respect of U.S. Patent 6,713,485.

(c) A certificate of correction was issued for U.S. Patent 6,713,485 and is attached hereto as **EXHIBIT 8A**. The certificate for correction states that the term of this patent subsequent to January 8, 2019 has been disclaimed. A copy of the terminal disclaimer is attached hereto as **EXHIBIT 8B.** A request for a second Certificate of Correction to delete Kathryn Jane Smith from the list of inventors was filed on October 7, 2005 and is currently pending. A copy of the request is attached hereto as **EXHIBIT 8C**.

(9) United States Patent 6,713,485 claims the active ingredient, lapatinib, in the approved product, TYKERB® Tablets. Applicant hereinbelow lists each applicable patent claim and demonstrates the manner in which each applicable claim reads on the approved product or method of using the approved product.

(a) Claim 1 as corrected in the Certificate of Correction reads as follows: A compound of the formula:



or salts or solvates thereof.

Claim 1 reads on the approved product, TYKERB® Tablets, because the active ingredient of the approved product, lapatinib, is a compound having the formula set forth in claim 1. Lapatinib is present in the approved product as the monohydrate of the ditosylate salt

(b) Claim 2 reads as follows: A pharmaceutical formulation, comprising: the compound of claim 1 or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers, diluents, or excipients.

Claim 2 reads on the approved product, TYKERB® Tablets, because the approved product is a pharmaceutical composition which contains the active ingredient lapatinib (a compound of claim 1), along with magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate, which are pharmaceutically acceptable carriers, diluents, or excipients.

(c) Claim 3 reads as follows: A method of treating a susceptible cancer in a human or animal subject mammal, comprising administering to said subject an effective amount of a compound as claimed in claim 1, wherein said cancer is breast cancer, gastric cancer or head and neck cancer.

Claim 3 reads on the approved product, TYKERB® Tablets, because the claim recites a method of using a compound of claim 1, which is lapatinib, the active ingredient of the approved product, in a method of treatment for breast cancer. The approved indication for lapatinib is the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including anthracycline, a taxane, and trastuzumab.

(d) Claim 4 reads as follows: A method as claimed in claim 3, wherein the susceptible cancer is breast cancer.

Claim 4 reads on the approved product, TYKERB® Tablets, because the claim recites a method of using a compound of claim 1, which is lapatinib, the active ingredient of the approved product, in a method of treatment for breast cancer. The approved indication for lapatinib is the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including anthracycline, a taxane, and trastuzumab.

(10) The relevant dates and information pursuant to 35 U.S.C 156(g) necessary to enable the Secretary of Health and Human Resources to determine the applicable regulatory review period are as follows:

a) Effective Date and Number of the IND
The first Investigational New Drug Application ("IND") for TYKERB® was submitted on December 6, 2000 and was assigned IND number 61,632. Pursuant to 21 C.F.R. § 312.40(b)(2), the IND became effective on January 5, 2001. See **EXHIBIT 9A**.

(b) Issue Date of Patent
US Patent No. 6,713,485 issued March 30, 2004 and claims a new drug and drug product. See **EXHIBIT 7**.

(c) Submission Date and Number of NDA
The NDA for TYKERB® Tablets was submitted on a rolling basis. The initial NDA submission was made on August 25, 2006, and the NDA was completed on September 13, 2006, and was designated as NDA No. 22-059. See **EXHIBIT 9B**.

(d) Approval Date of NDA
NDA No. 22-059 for TYKERB® Tablets was approved by the FDA on March 13, 2007. See **EXHIBIT 5**.

(11) A brief description of the significant activities undertaken by Applicant during both the IND and NDA regulatory periods is presented in a chronological form and is attached hereto as **EXHIBIT 9** (including **EXHIBITS 9A** and **9B**), "Due Diligence Log".

(a) The Due Diligence Log reflects significant communications with FDA during regulatory periods. Such communications include, but are not limited to: submission of preclinical reports; registration of clinical protocols and amendments thereof; registration of clinical investigators and amendments thereof; submission of adverse event reports; submission of IND Annual Reports, etc.

(b) Periods between such communications enumerated in the Due Diligence Log reflect Applicant's diligent undertaking of the necessary clinical studies and other activities required by the FDA in order to obtain approval for Applicant's product.

(12) Applicant is of the opinion that U.S. Patent 6,713,485 is eligible for a 628 day extension subject to the 14 year limitation pursuant to 36 U.S.C. § 156(c)(3).

(a) Applicant has satisfied the eligibility criteria necessary to obtain a patent term extension pursuant to 35 U.S.C. § 156.

(i) 35 U.S.C. § 156(a)
U.S. Patent No. 6,713,485 claims a drug product.

(ii) 35 U.S.C. § 156(a)(1)
The term of U.S. Patent No. 6,713,485 has not expired before the submission of application.

(iii) 35 U.S.C. § 156(a)(2)
The term of U.S. Patent No. 6,713,485 has never been extended.

(iv) 35 U.S.C. § 156(a)(3)
The application for extension is submitted by the agent of the owner of record in accordance with the requirements of 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 et seq.

(v) 35 U.S.C. § 156(a)(4)
The approved product, TYKERB® Tablets, has been subject to a regulatory review period before its commercial marketing or use.

(vi) 35 U.S.C. § 156(a)(5)(A)
The commercial marketing or use of the approved product, TYKERB® Tablets, after the regulatory review period is the first permitted commercial marketing or use of the approved product under the provisions under which such regulatory review period occurred.

(b) Applicant herewith, claims a patent term extension of 628 days for U.S. Patent No. 6,713,485 pursuant to 35 U.S.C. § 156(g) and subject to the limitations of 35 U.S.C. § 156(g)(6)(A) as follows:

(i) One-half the IND regulatory review period for the approved product beginning March 31, 2004 (the IND period occurring after the date of the issuance of U.S. Patent No. 6,713,485) and ending September 12, 2006 (one day prior to the date on which the NDA or the approved product was "initially submitted" pursuant to 21 C.F.R. § 60.22(f)), such period being equal to 447 days. See **Exhibit 10**.

(ii) The full term of the NDA regulatory review period commencing September 13, 2006 (the date NDA for the approved products was "initially submitted" pursuant to 21 C.F.R. § 60.22(f)) and ending on March 13, 2007 (the date on which NDA 22-059 was approved), such period being equal to 181 days. See **Exhibit 10**.

(iii) The sum of Items 12(b)(1) and 12(b)(2) is equal to 628 days. See **Exhibit 10**.

(c) Applicant herewith claims an extension expiry date of September 27, 2020 for U.S. Patent No. 6,713,485.

(i) The expiration of U.S. Patent 6,713,485 is January 8, 2019.

(ii) Extending the January 8, 2019 expiration date by 628 days would result in an expiration date of September 27, 2020. **See EXHIBIT 10.**

(13) The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension.

(14) The Commissioner of Patents is hereby authorized to charge deposit account number 07-1392 in the amount of $1,120.00 for receiving and acting upon this application for extension of term. In the event the actual fees due in connection with Applicant's application for patent term extension differ from the amount specified above, the Commissioner is hereby authorized to credit any overpayment or charge any underpayment to Applicants' deposit account number 07-1392.

(15) Inquiries and correspondences relating to this application for patent term extension are to be directed to:

John Lemanowicz
Senior Patent Counsel
SmithKline Beecham Corp.
Corporate Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-8247

(16) Applicants submit three original copies of the application papers.

(17) Submitted herewith is a Declaration by John Lemanowicz, Senior Patent Counsel for SmithKline Beecham Corp., which meets the criteria set forth in 37 C.F.R. § 1.730(b), and includes a Rule 3.73(b) certification on behalf of SmithKline Beecham Corporation, which establishes the right of SmithKline Beecham Corporation, as assignee, to take action in the Patent and Trademark Office in connection with this patent, including the naming of Applicant as its agent for purposes of filing this application, and grants power of attorney to the named registered patent attorneys.

The undersigned hereby certifies that this Application for Extension of Patent Term Under 35 U.S.C. 156, including Exhibits 1-11 is being submitted as triplicate originals.

Respectfully submitted,

By: _____

John Lemanowicz
Reg. No. 37,380
Attorney for Applicant
SmithKlineBeecham Corporation

05-04-07

10/071358

$

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 6,713,485

Issued: March 30, 2004

Inventors: Malcolm Clive Carter, George Stuart Cockerill, Stephen Barry Guntrip, Karen Elizabeth Lackey, Kathryn Jane Smith

Assignee: SmithKline Beecham Corp.

For: HETEROCYCLIC COMPOUNDS

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is an Application for Extension of a Patent Term under 35 U.S.C. 156 with regard to U.S. Patent No. 6,713,485.

The Commissioner of Patent and Trademarks is hereby authorized to charge deposit account number 07-1392 in the amount of $1,120.00 for receiving and acting upon this application for extension of term. In the event the actual fees due in connection with Applicant's application for patent term extension differ from the amount specified above, the Commissioner is hereby authorized to credit any overpayment or charge any underpayment to Applicants' deposit account number 07-1392.

Inquiries and correspondences relating to this application for patent term extension are to be directed to:

John Lemanowicz
Senior Patent Counsel
SmithKline Beecham Corp.
Corporate Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-8247

Respectfully submitted,

By: _____

John Lemanowicz
Reg. No. 37,380
Attorney for Applicant
SmithKline Beecham Corporation

CHECKLIST OF EXHIBITS FOR APPLICATION FOR PTE FOR TYKERB®

Exhibit 1A: Assignment from Lackey to GW
Exhibit 1B: Assignment from remaining inventors to GW
Exhibit 2: Articles of Merger
Exhibit 3: Assignment from SKB Corp to SKB Cork
Exhibit 4: Assignment from SKB Cork to SKB Corp.
Exhibit 5: FDA Approval Letter
Exhibit 6: Package insert
Exhibit 7: Copy of U.S. Patent No. 6,713,485
Exhibit 8A: Certificate of Correction
Exhibit 8B: Terminal Disclaimer
Exhibit 8C: Request for Second Certificate of Correction
Exhibit 9A: IND diligence log
Exhibit 9B: NDA diligence log
Exhibit 10: Patent Term Extension Calculations

EXHIBIT 1A

Assignment from Lackey to GW

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

MAY 26, 1999

PTAS

100982368A

GLAXO WELLCOME INC., PATENT COUNSEL
DAVID J. LEVY
FIVE MOORE DRIVE
PO BOX 13398
RTP NC 27709

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 03/01/1999

REEL/FRAME: 9804/0668
NUMBER OF PAGES: 6

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
KAREN ELIZABETH LACKEY

DOC DATE: 01/08/1999

ASSIGNEE:
GLAXO WELLCOME INC.
FIVE MOORE DRIVE
P.O. BOX 13398 GLOBAL INTELLECTUAL
PROPERTY DEPT.
RTP, NORTH CAROLINA 27709

ASSIGNEE:
GLAXO GROUP LIMITED
BERKELEY AVENUE
GLOBAL INTELLECTUAL PROPERTY DEPT.
GREENFORD, MIDDLESEX UB6 0NN

UNITED KINGDOM

SERIAL NUMBER: FILING DATE:
PATENT NUMBER: ISSUE DATE:
PCT NUMBER: EP9900048

SHARON LATIMER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

03-15-1999

US DEPARTMENT OF COMMERCE
Patent and Trademark Office

SHEET

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MRD 3.1.99

100982368

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Karen Elizabeth LACKEY

Additional name(s) of conveying party(ies) attached?

3. Nature of conveyance:

X Assignment Merger

Security Agreement Change of Name

Other _____

Execution Date: **January 8, 1999**

2. Name and address of receiving party(ies):

Name: **Glaxo Wellcome Inc.**

Internal Address: **Global Intellectual Property Dept.**

Street Address: **Five Moore Drive**
PO Box 13398
RTP, NC 27709

Additional name(s) & address(es) attached? **Yes** / No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the Express Mail date of the application is:.

A. Patent Application No.(s) Patent No.(s)

PCT/EP99/00048 filed on 08 January 1999

Additional numbers attached? Yes **X No**

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: **David J. Levy**
Patent Counsel

Internal Address: **Glaxo Wellcome Inc.**
Global Intellectual Property

Street Address: **Five Moore Drive**
PO Box 13398

City: **RTP** State: **NC** Zip: **27709**

6. Total number of applications and patents involved: **1**

7. Total fee (37 CFR 3.41):..... **$ 40.00** E
Enclosed

X Authorized to be charged to deposit account

8. Deposit account number: **07-1392**

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Elizabeth SELBY X Elizabeth Selby 23 February 1999
Name Signature Date

Total number of pages comprising cover sheet: **1 of 2**

Total number of pages including 2 cover sheets, attachments and documents = 6

03/01/1999 DNGUYEN 00000218 071392 EP9900048
01:FC:131 40.00 CH

Assignment

WHEREAS, I/we, **Malcolm Clive CARTER, George Stuart COCKERILL, Stephen Barry GUNTRIP, Kathryn Jane SMITH,** all citizens of the United Kingdom and **Karen Elizabeth LACKEY**, a citizen of the United States of America, respectively residing in Herts, United Kingdom; Maulden, Bedfordshire, United Kingdom; Hertford, Hertfordshire, United Kingdom; Bishop's Stortford, Hertfordshire, United Kingdom and Hillsborough, North Carolina, USA have invented or discovered certain improvements in **HETEROCYCLIC COMPOUNDS** hereinafter referred to as said invention and improvements for which a patent application GB9800569.7 was filed on 12 January 1998 the United Kingdom and for which an international PCT application is now being filed designating the United States of America and naming assignor as inventor, and in the United States only applicant/inventor. I hereby authorized and request that the filing date and application number of said PCT application, when known, be inserted here in parentheses

(PCT EP99/00048 filed 08 January 1999).

WHEREAS, GLAXO WELLCOME INC., a corporation organized and existing under and by virtue of the laws of the State of North Carolina and having its principal place of business at Five Moore Drive, Research Triangle Park, North Carolina 27709, USA, is desirous of acquiring the whole right, title and interest in and to said invention and improvements and said application, and in and to any Letters Patent to be obtained therefor, in the United States, its territories and possessions; and

WHEREAS, GLAXO GROUP Ltd., a company incorporated in England, whose registered office is at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 ONN, UK, is desirous of acquiring the whole right, title and interest in and to said invention and improvements, and in and to any applications for said invention and improvements and any Letters Patent to be obtained therefor, in all countries other than the United States, its territories and possessions;

NOW, THEREFORE, to all whom it may concern, be it known that I/we **Malcolm Clive CARTER, George Stuart COCKERILL, Stephen Barry GUNTRIP, Karen Elizabeth LACKEY, Kathryn Jane**

have sold, assigned and transferred, and by these presents do sell, assign and transfer my/our whole right, title and interest in and to said invention and improvements to said GLAXO WELLCOME INC., throughout the United States of America, its territories and possessions, and in and to said application and any extensions, reissues, continuations, continuations-in-part, and any divisions thereof, and in and to any and all Letters Patent of the United States of America;

AND, my/our whole right, title and interest in and to said invention and improvements to GLAXO GROUP Ltd., in all other countries throughout the world, and in to any applications in said other countries, and continuations-in-part, patents of addition, revalidation patents, patents of importation, registrations, and any renewals, extensions and divisions thereof, and in and to any and all Letters Patent of said all other countries which may be granted on said invention and improvements including any priority rights under the International Convention.

AND, I/we do hereby authorize and request the issue of any Letters Patent in the respective areas referred to, to said GLAXO WELLCOME INC. or GLAXO GROUP Ltd., as assignees of my/our whole right, title and interest in and to the same for the sole use and behoof of the said assignees, their successors and assigns as their interests appear herein;

AND, I/we warrant that I/we have not knowingly conveyed to others any right in said invention, improvements, applications or patents or any license to use the same or to make, use or sell anything embodying or utilizing said invention and improvements and that I/we have good right to assign the same to GLAXO WELLCOME INC. and GLAXO GROUP Ltd.;

AND, I/we the undersigned we **Malcolm Clive CARTER, George Stuart COCKERILL, Stephen Barry GUNTRIP, Karen Elizabeth LACKEY, Kathryn Jane SMITH** for the consideration aforesaid, do hereby agree that I/we or my/our executors or legal representatives, will provide information and make, execute and deliver any and all other instruments in writing, and any and all further acts, application papers, affidavits, assignments and other documents which may be necessary or desirable to more effectually secure to and vest in said GLAXO WELLCOME INC. and GLAXO GROUP Ltd., their successors and assigns, the whole right, title

Inventor: **Stepehn Barry GUNTRIP** **Date:**

State of:_____
County of:_____

On the date(s) indicated, before me personally came **Stepehn Barry GUNTRIP** known to me to be the individual(s) described in the foregoing Assignment and who acknowledged and executed the same in my presence.

Notary:_____

My Commission Expires:_____

Karen Lackey 1/8/99

Inventor: **Karen Elizabeth LACKEY** **Date:**

State of: NC
County of: Wake

On the date(s) indicated, before me personally came **Karen Elizabeth LACKEY** known to me to be the individual(s) described in the foregoing Assignment and who acknowledged and executed the same in my presence.

Notary: Elaine Martens

My Commission Expires: 2/5/2001

Inventor: **Kathryn Jane SMITH** **Date:**

State of:_____
County of:_____

On the date(s) indicated, before me personally came **Kathryn Jane SMITH** known to me to be the individual(s) described in the foregoing Assignment and who acknowledged and executed the same in my presence.

Notary:_____

My Commission Expires:_____

EXHIBIT 1B

Assignment from remaining inventors to GW

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

FEBRUARY 01, 2001

PTAS

101534333A

GLAXO WELLCOME INC.
DAVID J. LEVY
FIVE MOORE DRIVE
PO BOX 13398
RTP NC 27709

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 11/14/2000

REEL/FRAME: 011281/0024
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR''S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
CATRER, MALCOLM CLIVE — DOC DATE: 06/15/2000

ASSIGNOR:
COCKERILL, GEORGE STUART — DOC DATE: 06/15/2000

ASSIGNOR:
GUNTRIP, STEPHEN BARRY — DOC DATE: 06/15/2000

ASSIGNOR:
SMITH, KATHRYN JANE — DOC DATE: 06/15/2000

ASSIGNEE:
GLAXO WELLCOME INC.
FIVE MOORE DRIVE, PO BOX 13398
GLOBAL INTELLECTUAL PROPERTY
DEPARTMENT
RESEARCH TRIANGLE PARK
NORTH
CAROLINA
27709-03398

SERIAL NUMBER: 09582746
PATENT NUMBER:

FILING DATE: 06/30/2000
ISSUE DATE:

SAUNDRA BALLENGER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

101534333B

AUTHORIZATION TO CHARGE ADDITIONAL FEES TO DEPOSIT ACCOUNT

FEBRUARY 01, 2001

TO: OFFICE OF FINANCE

FROM: ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

SUBJECT: DEPOSIT ACCOUNT CHARGE(S)

CHARGE THE DEPOSIT ACCOUNT LISTED BELOW ADDITIONAL FEE(S) AS INDICATED BELOW. AUTHORIZATION TO CHARGE ADDITIONAL FEES HAS BEEN PROVIDED PER THE ATTACHED COVER SHEET, OR BY DIRECT CONTACT WITH THE CUSTOMER.

DEPOSIT ACCOUNT NUMBER: 071392
PROPERTY NUMBER: 09582746

IF YOU HAVE ANY QUESTIONS REGARDING THIS NOTICE, YOU MAY CONTACT THE INDIVIDUAL WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723.

SAUNDRA BALLENGER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

TRADEMARK SERVICE FEES:	FEE CODE:
RECORDING FIRST MARK	481
RECORDATION SECOND AND SUBSEQUENT MARK IN SAME DOCUMENT	482
LABOR CHARGES FOR SERVICES PER HOURS OR FRACTION THEREOF	484
UNSPECIFIED OTHER SERVICES	485

PATENT SERVICE FEES:	
RECORDING EACH PATENT ASSIGNMENT, AGREEMENT, OTHER PAPER, PER PROPERTY	581
LABOR CHARGES FOR SERVICES PER HOUR ($30) OR FRACTION THEREOF	584
UNSPECIFIED OTHER SERVICES	585

ASSIGNMENT

WHEREAS I/WE, Malcolm Clive CARTER, George Stuart COCKERILL, Stephen Barry GUNTRIP and Kathryn Jane SMITH, residing at Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (hereinafter called "the inventor(s)") have invented or discovered "**Bicyclic Heteraromatic Compounds as Protein Tyrosine Kinase Inhibitors**" (hereinafter called "the invention") for which an application for Letters Patent in the United States of America was originally filed as International Application No. PCT/EP99/00048 on 08 January 1999 (hereinafter called "the application"), and

WHEREAS the invention, being made in the circumstances set out in Section 39(1)(a) of the United Kingdom Patents Act 1977, belongs to my/our employer, namely GLAXO WELLCOME plc, a company incorporated in England whose registered address is Lansdowne House, Berkeley Square, London W1X 6BQ, England, and

WHEREAS GLAXO RESEARCH AND DEVELOPMENT LIMITED, a company incorporated in England whose registered address is Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, England, is desirous of acquiring from GLAXO WELLCOME plc the whole right, title and interest in and to the invention and the application, and

WHEREAS GLAXO WELLCOME plc and GLAXO RESEARCH AND DEVELOPMENT LIMITED have authorised and requested my/our making the application, and

WHEREAS GLAXO WELLCOME INC., a corporation organised and existing under and by virtue of the laws of the State of North Carolina and having its principal place of business at Five Moore Drive, Research Triangle Park, North Carolina 27709, USA is desirous of acquiring from GLAXO RESEARCH AND DEVELOPMENT LIMITED the whole right, title and interest in and to the invention and the application in respect of the United States of America;

NOW, THEREFORE, to all whom it may concern be it known that I/we, the inventor(s), hereby confirm the ownership by GLAXO WELLCOME plc of the invention and the application by operation of law under the United Kingdom Patents Act 1977 and, if under the law of the United States of America I/we the inventor(s) have any ownership right, title and interest in the invention and the application (which I/we do not believe to be the case and claim no ownership right, title or interest in the invention and the application based on the law of the United Kingdom), I/we the inventor(s) nevertheless hereby assign and transfer such ownership right, title and interest in and to the invention and the application to GLAXO WELLCOME plc. GLAXO WELLCOME plc in turn hereby assigns and transfers to GLAXO RESEARCH AND DEVELOPMENT LIMITED its whole right, title and interest in and to the invention and the application. GLAXO RESEARCH AND DEVELOPMENT LIMITED in turn hereby assigns and transfers to GLAXO WELLCOME INC. its whole right, title and interest in and throughout the United States of America in and to the invention and the application and in and to any priority rights in respect of the invention and the application and in and to any divisional application, continuation or continuation in part application thereof, and in and to any extension or re-issue thereof, and I/we the inventor(s) and GLAXO WELLCOME plc and GLAXO RESEARCH AND DEVELOPMENT LIMITED hereby authorise and request any patent arising therefrom in the United States of America be issued to GLAXO WELLCOME INC.

AND GLAXO WELLCOME plc and GLAXO RESEARCH AND DEVELOPMENT LIMITED hereby, and I/we the inventor(s) for myself/ourselves and my/our respective executors and legal representatives hereby, agree to provide information and make execute and deliver any and all other instruments in writing, and any and all further acts, applications, papers, affidavits, assignments and other documents which may be possible and are necessary or desirable to more effectually secure to and vest in GLAXO WELLCOME INC., its successors and assigns, the whole right, title and interest in and to the invention and the application hereby assigned and transferred in respect of the United States of America.

IT is hereby declared that each of the transactions hereby effected does not form part of a larger transaction or of a series of transactions in respect of which the amount or value, or the aggregate amount or value, of the consideration exceeds £60,000.

IN WITNESS whereof and with effect from the 12 day of January 1998 the inventor(s) and Graham George Brereton as Attorney of both GLAXO WELLCOME plc and GLAXO RESEARCH AND DEVELOPMENT LIMITED by virtue of Powers of Attorney granted by GLAXO WELLCOME plc and GLAXO RESEARCH AND DEVELOPMENT LIMITED respectively have hereunto set their respective hands.

SIGNED by Malcolm Clive CARTER:

15 June 2000

in the presence of: JOHN COFFIELD,

SIGNED by George Stuart COCKERILL:

15 June 2000

In the presence of: ~~RICHARD~~ STEPHEN SEAN FLACK

SIGNED by Stephen Barry GUNTRIP:

15 June 2000

In the presence of: PHILIP CHARLES BOX

SIGNED by Kathryn Jane SMITH:

15 June 2000

In the presence of: RICHARD MARTYN ANGELL

SIGNED by Graham George Brereton as the Attorney of each of Glaxo Wellcome plc and Glaxo Research and Development Limited:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 6,713,485

Issued: March 30, 2004

Inventors: Malcolm Clive Carter, George Stuart Cockerill, Stephen Barry Guntrip, Karen Elizabeth Lackey, Kathryn Jane Smith

Assignee: SmithKline Beecham Corp.

For: HETEROCYCLIC COMPOUNDS

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JOHN LEMANOWICZ. UNDER 37 C.F.R. § 1.730

Sir:

I, John Lemanowicz, residing in Wake County, North Carolina, declare as follows:

(1) I am a patent attorney authorized to practice before the United States Patent and Trademark Office; my registration number is 37,380.

(2) I make this declaration as Senior Patent Counsel for SmithKline Beecham Corporation, a corporation of the State of Pennsylvania, having a place of business at Five Moore Drive, Research Triangle Park, North Carolina, 27709, having general authority to act on its behalf in patent matters.

(3) Pursuant to 37 C.F.R. § 3.73(b) and 35 U.S.C. § 156(d)(1), SmithKline Beecham Corporation is the record owner and assignee of the entire right title and interest in and to US Patent No. 6,713,485 issued March 30, 2004 for HETEROCYCLIC COMPOUNDS by virtue of assignment of the parent application 09/582,746 (now U.S. Patent No. 6,727,256) to Glaxo Wellcome, Inc., recorded in the United States Patent and Trademark Office on March 1, 1999, Reel 009804, Frame 0668 and on November 14, 2000, Reel 011281, Frame 0024; subsequent corporate merger between Glaxo Wellcome, Inc. and SmithKline Beecham Corporation (recorded in the United States Patent and Trademark Office on May 2, 2005 on Reel 016500, Frame 0822), followed by an assignment of the instant patent to SmithKline Beecham (Cork) Ltd. on August 29, 2006, Reel 18184, frame

0080 and an assignment to SmithKline Beecham Corp. on December 20, 2006, frame 018654, frame 0335 (see EXHIBITS 1-4 to the above-referenced application).

(4) I have reviewed the evidentiary documents for the aforesaid chain of title and hereby certify pursuant to 37 C.F.R. § 3.73(b) that, to the best of my knowledge and belief, title is in SmithKline Beecham Corporation by virtue of the assignments and corporate merger noted in paragraph (3).

(5) I have reviewed and understand the contents of the Application submitted herewith on behalf of SmithKline Beecham Corporation, requesting a 628 day extension of the term of US Patent No. 6,713,485.

(6) I believe that US Patent No 6,713,485 is subject to extension pursuant to 37 C.F.R. §1.710.

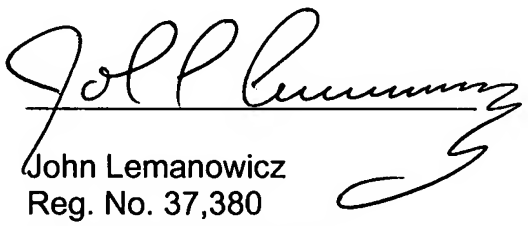
(7) I believe that a 628 day extension of the term of US Patent No. 6,713,485 is justified under 35 U.S.C. §156 and applicable regulations.

(8) I believe that US Patent No. 6,713,485, for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

(9) Any inquiries and correspondence relating to this Application for Patent Term Extension of US Patent No. 6,713,485 are to be directed to:

John Lemanowicz
Senior Patent Counsel
SmithKline Beecham Corp.
Corporate Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-8247

I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent 6,713,485 and any extensions thereof.



5/2/2007

John Lemanowicz
Reg. No. 37,380
Attorney for Applicant
SmithKlineBeecham Corporation

Date

EXHIBIT 2

Articles of Merger

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

GLAXO WELLCOME, INC.

Additional name(s) of conveying party(ies) attached? ☐ YES ☒ NO

3. Nature of conveyance:

☐ Assignment ☒ Merger
☐ Security Agreement ☐ Change of Name
☐ Other:

Execution Date: March 31, 2001

2. Name and address of receiving party(ies)

Name: SMITHKLINE BEECHAM CORPORATION

Internal Address:

Street Address: One Franklin Plaza

P.O. Box 7929

City: Philadelphia State: PA ZIP: 19101

Country: Postal Code:

Additional name(s) & address(es) attached? ☐ YES ☒ NO

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No(s).

B. Patent No.(s).

6,713,485 B2

6,727,256 B1

Additional numbers attached? ☐ YES ☒ NO

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: BIRCH, STEWART, KOLASCH & BIRCH, LLP

Street Address: P.O. BOX 747

City: FALLS CHURCH State: VA ZIP: 22040-0747

Country: USA

6. Total No. of applications/patents involved: two (2)

7. Total fee (37 C.F.R. § 3.41): $80.00

☒ Enclosed

☒ Authorized to be charged to deposit account, if no fee attached.

8. Deposit account number: 02-2448

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

MaryAnne Armstrong, #40,069
Name of Person Signing/Reg. No.

ma a
Signature

May 2, 2005
Date

Total number of pages including cover sheet, attachments, and document: four (4)

MAA/csm/geb

COMMONWEALTH OF PENNSYLVANIA

DEPARTMENT OF STATE

APRIL 05, 2001

TO ALL WHOM THESE PRESENTS SHALL COME, GREETING:

SMITHKLINE BEECHAM CORPORATION

I, Kim Pizzingrilli, Secretary of the Commonwealth of Pennsylvania do hereby certify that the foregoing and annexed is a true and correct photocopy of Articles of Merger restating the Articles of Incorporation in their entirety

which appear of record in this department

IN TESTIMONY WHEREOF, I have hereunto set my hand and caused the Seal of the Secretary's Office to be affixed, the day and year above written.

Kim Pizzingrilli

Secretary of the Commonwealth

DPOS

200124 - 955

MAR 3 0 2001

Microfilm Number _____

Filed with the Department of State on _____

Entity Number 33095

Secretary of the Commonwealth

ARTICLES OF MERGER-DOMESTIC BUSINESS CORPORATION

DSCB:15-1926 (Rev 99)

In compliance with the requirements of 15 Pa.C.S. § 1926 (relating to articles of merger or consolidation), the undersigned business corporations, desiring to effect a merger, hereby state that:

1. The name of the corporation surviving the merger is: SmithKline Beecham Corporation

2. (Check and complete one of the following):

X The surviving corporation is a domestic business corporation and the (a) address of its current registered office in this Commonwealth or (b) name of its commercial registered office provider and the county of venue is (the Department is hereby authorized to correct the following information to conform to the records of the Department):

(a) One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102 Phila.
Number and Street City State Zip County

(b) c/o: _____ _____
Name of Commercial Registered Office Provider County

For a corporation represented by a commercial registered office provider, the county in (b) shall be deemed the county in which the corporation is located for venue and official publication purposes.

___ The surviving corporation is a qualified foreign business corporation incorporated under the laws of _____ and the (a) address of its current registered office in this Commonwealth or (b) name of its commercial registered office provider and the county of venue is (the Department is hereby authorized to correct the following information to conform to the records of the Department):

(a) _____ _____ _____ _____
Number and Street City State Zip County

(b) c/o: _____ _____
Name of Commercial Registered Office Provider County

For a corporation represented by a commercial registered office provider, the county in (b) shall be deemed the county in which the corporation is located for venue and official publication purposes.

___ The surviving corporation is a nonqualified foreign business corporation incorporated under the laws of _____ and the address of its principal office under the laws of such domiciliary jurisdiction is:

_____ _____ _____ _____
Number and Street City State Zip

3. The name and the address of the registered office in this Commonwealth or name of its commercial registered office provider and the county of venue of each other domestic business corporation and qualified foreign business corporation which is a party to the plan of merger are as follows:

Name of Corporation	Address of Registered Office or Name of Commercial Registered Office Provider	County
Glaxo Wellcome Inc.	CT Corporation System	Philadelphia

200124 - 956

DSCB:15-1926 (Rev 90)-2

4. (Check, and if appropriate complete, one of the following):

___ The plan of merger shall be effective upon filing these Articles of Merger in the Department of State.

_X_ The plan of merger shall be effective on March 31, 2001 (Date) at 11:30 p.m. (Hour)

5. The manner in which the plan of merger was adopted by each domestic corporation is as follows:

Name of Corporation	Manner of Adoption
SmithKline Beecham Corporation	Adopted by the directors and shareholders pursuant to 15 Pa.C.S. § 1926(a).

6. (Strike out this paragraph if no foreign corporation is a party to the merger). The plan was authorized, adopted or approved, as the case may be, by the foreign business corporation (or each of the foreign business corporations) party to the plan in accordance with the laws of the jurisdiction in which it is incorporated.

7. (Check, and if appropriate complete, one of the following):

_X_ The plan of merger is set forth in full in Exhibit A attached hereto and made a part hereof.

___ Pursuant to 15 Pa.C.S. § 1901 (relating to omission of certain provisions from filed plans) the provisions, if any, of the plan of merger that amend or constitute the operative Articles of Incorporation of the surviving corporation as in effect subsequent to the effective date of the plan are set forth in full in Exhibit A attached hereto and made a part hereof. The full text of the plan of merger is on file at the principal place of business of the surviving corporation, the address of which is:

_____
Number and Street City State Zip County

IN TESTIMONY WHEREOF, the undersigned corporation or each undersigned corporation has caused these Articles of Merger to be signed by a duly authorized officer thereof this _____ day of March, 2001.

SMITHKLINE BEECHAM CORPORATION
(Name of Corporation)

BY: Donald F. Parman
(Signature)

TITLE: Donald F. Parman, Secretary

GLAXO WELLCOME INC.
(Name of Corporation)

BY: Paul A. Holcombe Jr.
(Signature)

TITLE: Paul A. Holcombe, Jr., Secretary

EXHIBIT 3

Assignment from SKB Corp. to SKB Cork

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

AUGUST 29, 2006

PTAS

500144458A

500144458A

GLAXOSMITHKLINE, CORP INTELLECTUAL PROP
FIVE MOORE DRIVE, PO BOX 13398
MAIN B475
RESEARCH TRIANGLE PA, NC 27709

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 08/29/2006

REEL/FRAME: 018184/0080
NUMBER OF PAGES: 9

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
SMITHKLINE BEECHAM CORPORATION

DOC DATE: 06/22/2006

ASSIGNEE:
SMITHKLINE BEECHAM (CORK) LIMITED
CURRABINNY
CARRIGALINE, COUNTY CORK, IRELAND

SERIAL NUMBER: 10342810
PATENT NUMBER:
TITLE: HETEROCYCLIC COMPOUNDS

FILING DATE: 01/15/2003
ISSUE DATE:

SERIAL NUMBER: 11050033
PATENT NUMBER:
TITLE: HETEROCYCLIC COMPOUNDS

FILING DATE: 02/03/2005
ISSUE DATE:

018184/0080 PAGE 2

SERIAL NUMBER: 10311678 FILING DATE: 03/31/2003
PATENT NUMBER: ISSUE DATE:
TITLE: QUINAZOLINE DITOSYLATE SALT COMPOUNDS

SERIAL NUMBER: 10466290 FILING DATE: 07/15/2003
PATENT NUMBER: ISSUE DATE:
TITLE: CANCER TREATMENT METHOD

SERIAL NUMBER: 10510542 FILING DATE: 10/07/2004
PATENT NUMBER: ISSUE DATE:
TITLE: CANCER TREATMENT METHOD COMPRISING ADMINISTERING AN ERB-FAMILY INHIBITOR AND A RAF AND/OR RAS INHIBITOR

SERIAL NUMBER: 09214267 FILING DATE: 12/31/1998
PATENT NUMBER: 6391874 ISSUE DATE: 05/21/2002
TITLE: FUSED HETEROCYCLIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS

SERIAL NUMBER: 10062647 FILING DATE: 01/31/2002
PATENT NUMBER: 6828320 ISSUE DATE: 12/07/2004
TITLE: HETEROCYCLIC COMPOUNDS

SERIAL NUMBER: 09582746 FILING DATE: 06/30/2000
PATENT NUMBER: 6727256 ISSUE DATE: 04/27/2004
TITLE: BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS

SERIAL NUMBER: 10071358 FILING DATE: 02/08/2002
PATENT NUMBER: 6713485 ISSUE DATE: 03/30/2004
TITLE: HETEROCYCLIC COMPOUNDS

ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

Assignment

WHEREAS, I/we **SMITHKLINE BEECHAM CORPORATION,** a corporation organized and existing under and by virtue of the laws of the State of Pennsylvania and having its principal place of business at One Franklin Plaza, PO Box 7929, Philadelphia, Pennsylvania 19101, USA, hereby assigns to, **SMITHKLINE BEECHAM (CORK) LIMITED**, a company organized and existing under and by virtue of the laws of Ireland and having its principal place of business at Currabinny, Carrigaline, County Cork, Ireland (Eire) , the entire right, title and interest in and to said inventions and improvements which are the subject of Appendix A attached hereto, and related applications and in and to any Letters Patent to be obtained therefore, in the United States, its territories and possessions;

NOW, THEREFORE, to all whom it may concern, be it known that **SMITHKLINE BEECHAM CORPORATION,** for good and valuable consideration unto me/us moving, the receipt whereof is hereby acknowledged, have sold, assigned and transferred, and by these presents do sell, assign and transfer my/our whole right, title and interest in and to said invention and improvements to said **SMITHKLINE BEECHAM (CORK) LIMITED**, throughout the United States of America, its territories and possessions, and in and to said application and any extensions, reissues, continuations, continuations-in-part, and any divisions thereof, and in and to any and all Letters Patent of the United States of America;

AND, I/we do hereby authorize and request the issue of any Letters Patent in the respective areas referred to said **SMITHKLINE BEECHAM (CORK) LIMITED** as assignees of my/our whole right, title and interest in and to the same for the sole use and behalf of the said assignees, their successors and assigns as their interests appear herein;

AND, I/we warrant that I/we have not knowingly conveyed to others any right in said invention, improvements, applications or patents or any license to use the same or to make, use or sell anything embodying or utilizing said invention and improvements and that I/we have good right to assign the same to **SMITHKLINE BEECHAM (CORK) LIMITED**;

AND, I/we the undersigned **SMITHKLINE BEECHAM CORPORATION**, for the consideration aforesaid, do hereby agree that I/we or my/our executors or legal representatives, will provide information and make, execute and deliver any and all other instruments in writing, and any and all further acts, application papers, affidavits, assignments and other documents which may be necessary or desirable to more effectually secure to and vest in said **SMITHKLINE BEECHAM (CORK) LIMITED**, their successors and assigns, the whole right, title and interest in and to the said invention and improvements, applications, Letters Patent, rights, title and interest hereby sold, assigned and conveyed, or intended so to be.

IN WITNESS whereof, Charles E. DADSWELL, as Attorney of each of **SMITHKLINE BEECHAM CORPORATION and SMITHKLINE BEECHAM (CORK) LIMITED** by virtue of Powers of Attorney granted by **SMITHKLINE BEECHAM CORPORATION and SMITHKLINE BEECHAM (CORK) LIMITED**, respectively has hereunto set his respective hand.

*SIGNED by the said **CHARLES E. DADSWELL** as the Attorney of each of **SMITHKLINE BEECHAM CORPORATION and SMITHKLINE BEECHAM (CORK) LIMITED:***

SMITHKLINE BEECHAM CORPORATION

Charles E. DADSWELL, Attorney

Date: 06/22/2006

SMITHKLINE BEECHAM (CORK) LIMITED

Charles E. DADSWELL, Attorney

Date: 06/22/2006

Appendix A

GSK Docket No.	Application No.	Filing date	Issued Patent No.	Issued Date
PG3119USw	09.214267	31-Dec 1998	6391874	21-May-2002
PG3119US2	10.062647	31-Jan-2002	6828320	07-Dec-2004
PG3416	09.582746	30-June 2002	6727256	27-Apr-2004
PG3416US2	10.071358	08-Feb-2002	6713485	30-Mar-2004
PG3416US3	10/342810	15-Jan-2003		
PG3416US4	11/050033	03-Feb-2005		
PU3969	10/311678	31-March 2003		
PU4257	10/466290	15-July 2003		
PU4725	10/510542	07 Oct 2004		

Power of Attorney

BY THIS POWER OF ATTORNEY. given this 23rd day of February two thousand and five **SMITHKLINE BEECHAM CORPORATION**, a company incorporated in Pennsylvania (Registration No. 3330395) and having its registered office at One Franklin Plaza, P.O. Box 7929, Philadelphia, Pennsylvania 19101, United States of America, (hereinafter called "the Company"), **HEREBY** appoints all and any of its Directors, Secretary and Assistant Secretary for the time being, and **DAVID ROBERTS, PETER JOHN GIDDINGS, ARTHUR WILLIAM RUSSELL TYRRELL, HUGH BAINFORDE DAWSON, WENDY ANNE FILLER, MICHAEL JOHN STOTT, PETER I. DOLTON, HELEN KAYE QUILLIN, MARCUS JONATHAN WILLIAM DALTON, CHARLES M. KINZIG, STEPHEN VENETIANER, THEODORE R. FURMAN, MARY E. McCARTHY, EDWARD R. GIMMI, CHARLES EDWARD DADSWELL, ROBERT H. BRINK, and FRANK P. GRASSLER** jointly and severally to be its true and lawful agents and attorneys (hereinafter called "the Attorneys") on behalf and in the name of the Company or otherwise to do, perform, exercise or execute or concur with any other person or persons in doing, performing or exercising in or for any country or countries or jurisdiction in any part of the world all or any of the following powers, acts, deeds and things in connection with: letters patent, including extensions thereto; utility models; copyrights; trademark registrations; trademarks; trade names; trade dress; logos; design rights; designs and all rights analogous thereto and all applications therefor and any other forms whatsoever of intellectual property rights; including know-how, all of which are hereinafter called "Intellectual Property Rights", that is to say:

1. In any country or countries or jurisdiction in any part of the world to make application or cause application to be made for the grant or issue or transfer to the Company or registration in its name of Intellectual Property Rights and to take all steps necessary for the same to be prosecuted, maintained, withdrawn, renewed, enforced, defended or extended.

2. As the act and deed of the Company to sign, seal, deliver and execute all or any assignments or assurances, licences to the Company of or under any Intellectual Property Rights or the right to and interest in any inventions to be the subject of Intellectual Property Rights for the purpose of fully and effectually vesting and transferring the same in and to the Company.

3. As the act and deed of the Company to sign and execute all or any assignments and acceptances of the transfer or assignment of such rights, and also any licences, sub-licences and consents from the Company of or under any Intellectual Property Rights or the right to and interest in any invention to be the subject of Intellectual Property Rights, for the purpose of fully and effectually vesting transferring or granting the same in and to any entity, whether in the United Kingdom or elsewhere, in so far as such documents can be executed without the Company's seal being affixed thereto. For purposes of this Power of Attorney, the terms "entity" means, and includes, any person, firm or company or group of persons or unincorporated body.

4. To give undertakings or assurances to third parties and to any Trademark Registry or official intellectual property agency or governmental department or otherwise responsible for the registration or protection of trademarks, trade names, trade dress, logos, design rights or designs for the purpose of best protecting or ensuring the co-existence of the Company's rights to trademarks, trade names, trade dress, logos, design rights or designs.

5. To commence, prosecute and defend any proceedings or applications whether judicial or extra judicial relating to Intellectual Property Rights and to maintain, withdraw or settle the same.

6. For and in connection with any Intellectual Property Rights to sign, seal, deliver and execute any Power of Attorney or other deed or document authorising any agent, including trademark and patent agents and attorneys, to act on behalf of the Company.

7. To apply for the registration, amendment or cancellation of user rights in respect of any trademark or trade name.

8. To act in regard to all official communications which may now or hereafter be addressed to the Attorneys relating to Intellectual Property Rights or the renewal thereof in such manner that the Attorneys may be recognised as the authorised agent(s) of the Company in all proceedings in relation thereto.

9. For all or any of the purposes contained herein as the act and deed of the Company to sign, seal, deliver, execute and do all such documents, deeds, agreements, instruments and to do such acts as shall be requisite or may be deemed proper for or in relation to the said purposes.

10. This Power of Attorney shall expire on December 31, 2006

AND THE COMPANY HEREBY RATIFIES and confirms and agrees to ratify and confirm all and whatsoever the Attorneys or any person, persons, firm or company appointed by them shall lawfully do or have done by virtue of the authorities herein contained

AND THE COMPANY HEREBY DECLARES that all instruments executed under and by virtue of this Power shall be as valid and effectual as if sealed by the Common Seal of the Company.

IN WITNESS whereof **SMITHKLINE BEECHAM CORPORATION** has caused its Common Seal to be hereunto affixed the day and year first before written

The **COMMON SEAL** of)
SMITHKLINE BEECHAM CORPORATION)
was hereto affixed in the presence of:)

Donald F. Parman

Donald F. Parman
Vice President and Secretary

Power of Attorney

BY THIS POWER OF ATTORNEY given this 30th day of July two thousand and two **SMITHKLINE BEECHAM (CORK) LIMITED**, a company incorporated in Eire (Registration No. 217028) and having its registered office at Currabinny, Carrigaline, County Cork, Eire (hereinafter called "the Company"), **HEREBY** appoints all and any of its Directors, Secretary and Assistant Secretary for the time being, and **DAVID ROBERTS, PETER JOHN GIDDINGS, ARTHUR WILLIAM RUSSELL TYRRELL, HUGH BAINFORDE DAWSON, BRIAN JOHN RUSSELL, DAVID MARTIN WATERS, HELEN QUILLIN, CHARLES KINZIG, STEPHEN VENETIANER, DAVID LEVY** and **CHARLES E. DADSWELL** jointly and severally to be its true and lawful agents and attorneys (hereinafter called "the Attorneys") on behalf and in the name of the Company or otherwise to do, perform, exercise or execute or concur with any other person or persons in doing, performing or exercising in or for any country or countries or jurisdiction in any part of the world all or any of the following powers, acts, deeds and things in connection with: letters patent, including extensions thereto; utility models; copyrights; trademark registrations; trademarks; trade names; trade dress; logos; design rights; designs and all rights analogous thereto and all applications therefor and any other forms whatsoever of intellectual property rights; including know-how, all of which are hereinafter called "Intellectual Property Rights", that is to say:

1. In any country or countries or jurisdiction in any part of the world to make application or cause application to be made for the grant or issue or transfer to the Company or registration in its name of Intellectual Property Rights and to take all steps necessary for the same to be prosecuted, maintained, withdrawn, renewed, enforced, defended or extended.

2. As the act and deed of the Company to sign, seal, deliver and execute all or any assignments or assurances, licences to the Company of or under any Intellectual Property Rights or the right to and interest in any inventions to be the subject of Intellectual Property Rights for the purpose of fully and effectually vesting and transferring the same in and to the Company.

3. As the act and deed of the Company to sign and execute all or any assignments and acceptances of the transfer or assignment of such rights, and also any licences, sub-licences and consents from the Company of or under any Intellectual Property Rights or the right to and interest in any invention to be the subject of Intellectual Property Rights, for the purpose of fully and effectually vesting transferring or granting the same in and to any entity, whether in the United Kingdom or elsewhere, in so far as such documents can be executed without the Company's seal being affixed thereto. For purposes of this Power of Attorney, the terms "entity" means, and includes, any person, firm or company or group of persons or unincorporated body.

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5. To commence, prosecute and defend any proceedings or applications whether judicial or extra judicial relating to Intellectual Property Rights and to maintain, withdraw or settle the same.

6. For and in connection with any Intellectual Property Rights to sign, seal, deliver and execute any Power of Attorney or other deed or document authorising any agent, including trademark and patent agents and attorneys, to act on behalf of the Company.

TO ALL WHOM THESE PRESENTS SHALL COME:

I, FRANCIS D. DALY, of 12 South Mall in the City of the County of Cork, Notary Public, duly authorised, admitted and sworn and practising at 12 South Mall in the City of Cork, DO HEREBY CERTIFY that on this the 8th day of August 2002 at 12 South Mall in the County of Cork before me personally appears Joe Donovan, to me known, who being duly sworn by me deposes and says: that he is the Secretary of Smithkline Beecham (Cork) Limited the company named in and which executed under its common seal the annexed document constituting or described as a Power of Attorney; that he knows the seal of the said company; that the seal affixed to the said document is the common seal of Smithkline Beecham (Cork) Limited; that the seal was affixed to the said document by authority of the Board of Directors of Smithkline Beecham (Cork) Limited and that he Joe Donovan signed his name to the document in conjunction with the sealing thereof by like authority and in conformity with the provisions of the Articles of Association of Smithkline Beecham (Cork) Limited relating to the use and application of the common seal.

Joe Donovan

Subscribed and sworn before me by the said Joe Donovan at 12 South Mall in the City of the County of Cork this 8th day of August 2002.

Francis D. Daly
RONAN DALY JERMYN

WHEREOF an Act being required of me the said Notary, I have IN FAITH AND TESTIMONY set my hand and affixed my Official Seal at 12 South Mall in the City of the County of Cork this 8th day of August 2002.

Francis D. Daly
NOTARY PUBLIC

Electronic Patent Assignment System

Confirmation Receipt

Your assignment has been received by the USPTO.
The coversheet of the assignment is displayed below:

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
SMITHKLINE BEECHAM CORPORATION	06/22/2006

RECEIVING PARTY DATA

Name:	SMITHKLINE BEECHAM (CORK) LIMITED
Street Address:	Currabinny
City:	Carrigaline, County Cork
State/Country:	IRELAND

PROPERTY NUMBERS Total: 9

Property Type	Number
Patent Number:	6391874
Patent Number:	6828320
Patent Number:	6727256
Patent Number:	6713485
Application Number:	10342810
Application Number:	11050033
Application Number:	10311678
Application Number:	10466290

Application Number:	10510542

CORRESPONDENCE DATA

Fax Number:	(919)483-7977
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.	
Phone:	919-483-2252
Email:	elaine.x.martens@gsk.com
Correspondent Name:	GlaxoSmithKline, Corp Intellectual Prop
Address Line 1:	Five Moore Drive, PO Box 13398
Address Line 2:	Main B475
Address Line 4:	Research Triangle Pa, NORTH CAROLINA 27709

DOMESTIC REPRESENTATIVE

Name:	
Address Line 1:	
Address Line 2:	
Address Line 3:	
Address Line 4:	

NAME OF SUBMITTER:	John Lemanowicz
Signature:	/John Lemanowicz/
Date:	08/29/2006

Total Attachments: 7
source=Appendix A Assignment#page1.tif
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source=Appendix A Assignment#page4.tif
source=Appendix A Assignment#page5.tif
source=Appendix A Assignment#page6.tif
source=Appendix A Assignment#page7.tif

RECEIPT INFORMATION

EPAS ID:	PAT150605
Receipt Date:	08/29/2006
Fee Amount:	$360

Return to home page

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EXHIBIT 4

Assignment from SKB Cork to SKB Corp.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECEMBER 20, 2006

PTAS

500196746A

500196746A

GLAXOSMITHKLINE, CORP INTELLECTUAL PROP
FIVE MOORE DRIVE, PO BOX 13398
MAIN 475
RESEARCH TRIANGLE PA, NC 27709

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 12/20/2006

REEL/FRAME: 018654/0335
NUMBER OF PAGES: 5

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
SMITHKLINE BEECHAM (CORK) LIMITED

DOC DATE: 12/19/2006

ASSIGNEE:
SMITHKLINE BEECHAM CORPORATION
ONE FRANKLIN PLAZA, PO BOX 7929
PHILADELPHIA, PENNSYLVANIA 19101

SERIAL NUMBER: 10342810
PATENT NUMBER:
TITLE: HETEROCYCLIC COMPOUNDS

FILING DATE: 01/15/2003
ISSUE DATE:

SERIAL NUMBER: 11532926
PATENT NUMBER:
TITLE: HETEROCYCLIC COMPOUNDS

FILING DATE: 09/19/2006
ISSUE DATE:

018654/0335 PAGE 2

SERIAL NUMBER: 11558616 FILING DATE:
PATENT NUMBER: ISSUE DATE:
TITLE: QUINAZOLINE DITOSYLATE SALT COMPOUNDS

SERIAL NUMBER: 11548413 FILING DATE:
PATENT NUMBER: ISSUE DATE:
TITLE: CANCER TREATMENT METHOD

SERIAL NUMBER: 10510542 FILING DATE: 10/07/2004
PATENT NUMBER: ISSUE DATE:
TITLE: CANCER TREATMENT METHOD COMPRISING ADMINISTERING AN ERB-FAMILY INHIBITOR AND A RAF AND/OR RAS INHIBITOR

SERIAL NUMBER: 10595691 FILING DATE:
PATENT NUMBER: ISSUE DATE:
TITLE: CANCER TREATMENT METHOD

SERIAL NUMBER: 09214267 FILING DATE: 12/31/1998
PATENT NUMBER: 6391874 ISSUE DATE: 05/21/2002
TITLE: FUSED HETEROCYCLIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS

SERIAL NUMBER: 10062647 FILING DATE: 01/31/2002
PATENT NUMBER: 6828320 ISSUE DATE: 12/07/2004
TITLE: HETEROCYCLIC COMPOUNDS

SERIAL NUMBER: 09582746 FILING DATE: 06/30/2000
PATENT NUMBER: 6727256 ISSUE DATE: 04/27/2004
TITLE: BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS

SERIAL NUMBER: 10071358 FILING DATE: 02/08/2002
PATENT NUMBER: 6713485 ISSUE DATE: 03/30/2004
TITLE: HETEROCYCLIC COMPOUNDS

SERIAL NUMBER: 11050033 FILING DATE: 02/03/2005
PATENT NUMBER: 7109333 ISSUE DATE: 09/19/2006
TITLE: HETEROCYCLIC COMPOUNDS

SERIAL NUMBER: 10311678 FILING DATE: 03/31/2003
PATENT NUMBER: 7157466 ISSUE DATE: 01/02/2007
TITLE: QUINAZOLINE DITOSYLATE SALT COMPOUNDS

SERIAL NUMBER: 10466290 FILING DATE: 07/15/2003
PATENT NUMBER: 7141576 ISSUE DATE: 11/28/2006
TITLE: CANCER TREATMENT METHOD

LAZENA MARTIN, EXAMINER
ASSIGNMENT SERVICES BRANCH

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

12/20/2006
500196746

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
SMITHKLINE BEECHAM (CORK) LIMITED	12/19/2006

RECEIVING PARTY DATA

Name:	SMITHKLINE BEECHAM CORPORATION
Street Address:	One Franklin Plaza, PO Box 7929
City:	Philadelphia
State/Country:	PENNSYLVANIA
Postal Code:	19101

PROPERTY NUMBERS Total: 13

Property Type	Number
Patent Number:	6391874
Patent Number:	6828320
Patent Number:	6727256
Patent Number:	6713485
Application Number:	10342810
Patent Number:	7109333
Application Number:	11532926
Patent Number:	7157466
Application Number:	11558616
Patent Number:	7141576
Application Number:	11548413
Application Number:	10510542
Application Number:	10595691

CH $520.00 6391874

CORRESPONDENCE DATA

Fax Number:	(919)483-7977
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.	
Phone:	919-483-2252
Email:	elaine.x.martens@gsk.com
Correspondent Name:	GlaxoSmithKline, Corp Intellectual Prop
Address Line 1:	Five Moore Drive, PO Box 13398
Address Line 2:	Main 475
Address Line 4:	Research Triangle Pa, NORTH CAROLINA 27709

NAME OF SUBMITTER:	John Lemanowicz

Total Attachments: 3
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source=SBCORK assign SBC#page3.tif

Facsimile Transmission

This company uses RightFAX® fax server software from RightFAX, Inc.

From:

Name: USPTO ASSIGNMENT DIVISION
Fax Number:
Voice Phone: 571-272-3350

To:

Name: GLAXOSMITHKLINE, CORP INTELLECTUAL PROP
Company: FIVE MOORE DRIVE, PO BOX 13398
Fax Number: 19194837977
Voice Phone:

Fax Notes:

Pg#	Description
1	Cover Page
2	203.TXT
5	Document 1, Batch 812555

PTAS FAX PROCESSING

Date and time of transmission: Thursday, December 21, 2006 6:46:12 AM
Number of pages including this cover sheet: 06

Assignment

WHEREAS, I/we **SMITHKLINE BEECHAM (CORK) LIMITED,** a corporation organized and existing under and by virtue of the laws of the Ireland and having its principal place of business at Currabinny, Carrigaline, Count Cork, Ireland, hereby assigns to, **SMITHKLINE BEECHAM CORPORATION,** a corporation organized and existing under and by virtue of the laws of the State of Pennsylvania and having its principal place of business at One Franklin Plaza, PO Box 7929, Philadelphia, Pennsylvania 19101, USA, the entire right, title and interest in and to said inventions and improvements which are the subject of **Appendix A** attached hereto, and related applications and in and to any Letters Patent to be obtained therefore, in the United States, its territories and possessions;

NOW, THEREFORE, to all whom it may concern, be it known that **SMITHKLINE BEECHAM (CORK) LIMITED,** for good and valuable consideration unto me/us moving, the receipt whereof is hereby acknowledged, have sold, assigned and transferred, and by these presents do sell, assign and transfer my/our whole right, title and interest in and to said invention and improvements to said **SMITHKLINE BEECHAM CORPORATION**, throughout the United States of America, its territories and possessions, and in and to said application and any extensions, reissues, continuations, continuations-in-part, and any divisions thereof, and in and to any and all Letters Patent of the United States of America;

AND, I/we do hereby authorize and request the issue of any Letters Patent in the respective areas referred to said **SMITHKLINE BEECHAM CORPORATION** as assignees of my/our whole right, title and interest in and to the same for the sole use and behalf of the said assignees, their successors and assigns as their interests appear herein;

AND, I/we warrant that I/we have not knowingly conveyed to others any right in said invention, improvements, applications or patents or any license to use the same or to make, use or sell anything embodying or utilizing said invention and improvements and that I/we have good right to assign the same to **SMITHKLINE BEECHAM CORPORATION**;

AND, I/we the undersigned **SMITHKLINE BEECHAM (CORK) LIMITED**, for the consideration aforesaid, do hereby agree that I/we or my/our executors or legal representatives, will provide information and make, execute and deliver any and all other instruments in writing, and any and all further acts, application papers, affidavits, assignments and other documents which may be necessary or desirable to more effectually secure to and vest in said **SMITHKLINE BEECHAM CORPORATION**, their successors and assigns, the whole right, title and interest in and to the said invention and improvements, applications, Letters Patent, rights, title and interest hereby sold, assigned and conveyed, or intended so to be.

IN WITNESS whereof, Charles E. DADSWELL, as Attorney of each of **SMITHKLINE BEECHAM (CORK) LIMITED and SMITHKLINE BEECHAM CORPORATION** by virtue of Powers of Attorney granted **by SMITHKLINE BEECHAM (CORK) LIMITED and SMITHKLINE BEECHAM CORPORATION** respectively has hereunto set his respective hand.

SIGNED by the said ***CHARLES E. DADSWELL*** *as the Attorney of each of* **SMITHKLINE BEECHAM (CORK) LIMITED** ***and*** **SMITHKLINE BEECHAM CORPORATION:**

SMITHKLINE BEECHAM (CORK) LIMITED

Date: 12/15/2006

Charles E. DADSWELL, Attorney

SMITHKLINE BEECHAM CORPORATION

Date: 12/15/2006

Charles E. DADSWELL, Attorney

APPENDIX A

GSK Docket No.	US Serial Number	Filing Date	Patent Number	Issue Date
PG3119USw	09/214267	31-Dec-1998	6391874	21-May-2002
PG3119US2	10/062647	31-Jan-2002	6828320	07-Dec-2004
PG3416USw	09/582746	30-June-2002	6727256	27-Apr-2004
PG3416US2	10/071358	08-Feb-2002	6713485	30-Mar-2004
PG3416US3	10/342810	15-Jan-2003		
PG3416US4	11/050033	03-Feb-2005	7109333	19 Sep-2006
PG3416US5	11/532926	19-Sep-2006		
PU3969USw	10/311678	31-March 2003	7157466	02- Jan- 2007
PU3969US2	11/558616	10-Nov-2006		
PU4257USw	10/466290	15-July-2003	7141576	28-Nov-2006
PU4257US1	11/548413	11-Oct-2006		
PU4725USw	10/510542	07-Oct-2004		
PR60548	10/595691	05-May-2006		

PATENT ASSIGNMENT

Electronic Version v1.1
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SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
SMITHKLINE BEECHAM (CORK) LIMITED	12/19/2006

RECEIVING PARTY DATA

Name:	SMITHKLINE BEECHAM CORPORATION
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City:	Philadelphia
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Postal Code:	19101

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Patent Number:	7109333
Application Number:	11532926
Patent Number:	7157466
Application Number:	11558616
Patent Number:	7141576
Application Number:	11548413

Application Number:	10510542
Application Number:	10595691

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Fax Number: (919)483-7977
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 919-483-2252
Email: elaine.x.martens@gsk.com
Correspondent Name: GlaxoSmithKline, Corp Intellectual Prop
Address Line 1: Five Moore Drive, PO Box 13398
Address Line 2: Main 475
Address Line 4: Research Triangle Pa, NORTH CAROLINA 27709

NAME OF SUBMITTER:	John Lemanowicz
Signature:	/John Lemanowicz/
Date:	12/20/2006

Total Attachments: 3
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RECEIPT INFORMATION

EPAS ID:	PAT204059
Receipt Date:	12/20/2006
Fee Amount:	$520

EXHIBIT 5

FDA Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-059

SmithKlineBeecham Corporation d/b/a GlaxoSmithKline
2301 Renaissance Blvd., Building 510
P.O. Box 61540
King of Prussia, PA 19406-2772

Attention: Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Swenson:

Please refer to your new drug application (NDA) dated September 13, 2006, received September 13, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TYKERB® (lapatinib) tablets, 250 mg.

We acknowledge receipt of your submissions dated October 4, 11, 23, 26, 30 and 31, 2006; November 2, 9, 10 (2), 15, 17 (3), 21 (2), 27, and 30, 2006; December 1, 8, 13, 18, and 22 (5), 2006; January 9, 11, 18, 19, 24, and 29, 2007; February 1, 6 (2), 26, 2007; March 7 (2), 8 (2), and 12, 2007.

This new drug application provides for the use of TYKERB® in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane and trastuzumab.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We remind you of your postmarketing study commitments in your submission dated March 7, 2007. These commitments are listed below.

1. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 3A4 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of midazolam. A positive finding in this study may initiate a need for further studies.

Protocol Submission:	October 1, 2005
Study Start:	Ongoing
Final Report Submission:	June 2008

2. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 2C8 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of paclitaxel or rosiglitazone. A positive finding in this study may initiate a need for further studies.

Protocol Submission: October 7, 2002
Study Start: Ongoing
Final Report Submission: June 2007

3. **Description of Commitment:** Based upon the ability of lapatinib to act as a Pgp inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of digoxin. A positive finding in this study may initiate a need for further studies.

Protocol Submission: September 2007
Study Start: November 2007
Final Report Submission: December 2009

4. **Description of Commitment:** GSK commits to submitting the results of the survival analysis of Study EGF100151 at 75% of the events.

Protocol Submission: November 2003
Study Start: Ongoing
Final Report Submission: June 2008

All applications for new active ingredients, new dosage forms, new indications, new routes of administration and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, and for the patient package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 22-059.**" Approval of this submission by FDA is not required before the labeling is used.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text/submitted labeling dated March 13, 2007. Upon

receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

Promotional materials should be submitted, in duplicate, directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

As discussed in our November 16, 2006 teleconference, your proposed Chemistry, Manufacturing and Controls (CMC) Regulatory Agreement, submitted as part of the CMC pilot program, was not received and is not part of this approval action. Existing regulations and guidances should be followed, as appropriate, for all post-approval CMC changes.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Office Director
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure-Label

EXHIBIT 6

Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYKERB safely and effectively. See full prescribing information for TYKERB.

TYKERB® (lapatinib) tablets
Initial U.S. Approval: 2007

INDICATIONS AND USAGE

TYKERB, a kinase inhibitor, is indicated in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage of TYKERB is 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m^2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21 day cycle. (2.1)

- TYKERB should be taken at least one hour before or one hour after a meal. However, capecitabine should be taken with food or within 30 minutes after food. (2.1)
- TYKERB should be taken once daily. Do not divide daily doses of TYKERB. (2.1, 12.3)
- Modify dose for cardiac and other toxicities, severe hepatic impairment, and CYP3A4 drug interactions. (2.2)

DOSAGE FORMS AND STRENGTHS

250 mg tablets (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Decreases in left ventricular ejection fraction have been reported. Confirm normal LVEF before starting TYKERB and continue evaluations during treatment. (5.1)
- Dose reduction in patients with severe hepatic impairment should be considered. (2.2, 5.2, 8.7)
- Diarrhea, including severe diarrhea, has been reported during treatment. Manage with anti-diarrheal agents, and replace fluids and electrolytes if severe. (5.3)
- Lapatinib prolongs the QT interval in some patients. Consider ECG and electrolyte monitoring. (5.4)
- Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking TYKERB. (5.5)

ADVERSE REACTIONS

The most common (>20%) adverse reactions during treatment with TYKERB plus capecitabine were diarrhea, palmar-plantar erythrodysesthesia, nausea, rash, vomiting, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- TYKERB is likely to increase exposure to concomitantly administered drugs which are metabolized by CYP3A4 or CYP2C8. (7.1)
- Avoid strong CYP3A4 inhibitors. If unavoidable, consider dose reduction of TYKERB in patients coadministered a strong CYP3A4 inhibitor. (2.2, 7.2)
- Avoid strong CYP3A4 inducers. If unavoidable, consider gradual dose increase of TYKERB in patients coadministered a strong CYP3A4 inducer. (2.2, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: March 2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TYKERB is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of TYKERB is 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m^2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21 day cycle. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily; dividing the daily dose is not recommended *[see Clinical Pharmacology (12.3)]*. Capecitabine should be taken with food or within 30 minutes after food. If a day's dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs.

2.2 Dose Modification Guidelines

Cardiac Events: TYKERB should be discontinued in patients with a decreased left ventricular ejection fraction (LVEF) that is grade 2 or greater by NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and in patients with an LVEF that drops below the institution's lower limit of normal *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*. TYKERB may be restarted at a reduced dose (1,000 mg/day) after a minimum of 2 weeks if the LVEF recovers to normal and the patient is asymptomatic.

Hepatic Impairment: Patients with severe hepatic impairment (Child-Pugh Class C) should have their TYKERB dose reduced. A dose reduction to 750 mg/day in patients with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the normal range and should be considered. However, there is no clinical data with this dose adjustment in patients with severe hepatic impairment.

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit may also increase plasma concentrations of lapatinib and should be avoided. If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inhibitors and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is

discontinued, a washout period of approximately 1 week should be allowed before the lapatinib dose is adjusted upward to the indicated dose. *[See Drug Interactions (7.2).]*

Concomitant Strong CYP3A4 Inducers: The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day based on tolerability. This dose of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inducers and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the lapatinib dose should be reduced to the indicated dose. *[See Drug Interactions (7.2).]*

Other Toxicities: Discontinuation or interruption of dosing with TYKERB may be considered when patients develop greater than or equal to grade 2 NCI CTC toxicity and can be restarted at 1,250 mg/day when the toxicity improves to grade 1 or less. If the toxicity recurs, then TYKERB should be restarted at a lower dose (1,000 mg/day).

See manufacturer's prescribing information for capecitabine dosage adjustment guidelines in the event of toxicity.

3 DOSAGE FORMS AND STRENGTHS

250 mg tablets — oval, biconvex, and orange, film-coated with GS XJG debossed on one side.

4 CONTRAINDICATIONS

None.

See manufacturer's prescribing information for capecitabine contraindications.

5 WARNINGS AND PRECAUTIONS

5.1 Decreased Left Ventricular Ejection Fraction

TYKERB has been reported to decrease LVEF *[see Adverse Reactions (6.1)]*. In the randomized clinical trial, the majority (>60%) of LVEF decreases occurred within the first 9 weeks of treatment; however, data on long-term exposure are limited. Caution should be taken if TYKERB is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with TYKERB to ensure that the patient has a baseline LVEF that is within the institution's normal limits. LVEF should continue to be evaluated during treatment with TYKERB to ensure that LVEF does not decline below the institution's normal limits *[see Dosage and Administration (2.2)]*.

5.2 Patients with Severe Hepatic Impairment

If TYKERB is to be administered to patients with severe hepatic impairment, dose reduction should be considered *[see Dosage and Administration (2.2) and Use in Specific Populations (8.7)]*.

5.3 Diarrhea

Diarrhea, including severe diarrhea, has been reported during treatment with TYKERB *[see Adverse Reactions (6.1)]*. Proactive management of diarrhea with anti-diarrheal agents is important. Severe cases of diarrhea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of therapy with TYKERB.

5.4 QT prolongation

QT prolongation measured by automated machine-read evaluation of ECG was observed in an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients *[see Clinical Pharmacology (12.4)]*. Lapatinib should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to lapatinib administration. The prescriber should consider baseline and on-treatment electrocardiograms with QT measurement.

5.5 Pregnancy

Pregnancy Category D

TYKERB can cause fetal harm when administered to a pregnant woman. In a study where pregnant rats were dosed with lapatinib during organogenesis and through lactation, at a dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC), 91% of the pups had died by the fourth day after birth, while 34% of the 60 mg/kg/day pups were dead. The highest no-effect dose for this study was 20 mg/kg/day (approximately equal to the human clinical exposure based on AUC).

Lapatinib was studied for effects on embryo-fetal development in pregnant rats and rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects; however, minor anomalies (left-sided umbilical artery, cervical rib, and precocious ossification) occurred in rats at the maternally toxic dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (approximately 0.07 and 0.2 times the human clinical exposure, respectively, based on AUC) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased fetal body weights and minor skeletal variations.

There are no adequate and well-controlled studies with TYKERB in pregnant women. Women should be advised not to become pregnant when taking TYKERB. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety of TYKERB has been evaluated in more than 3,500 patients in clinical trials. The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was

evaluated in 198 patients in a randomized, Phase 3 trial. *[See Clinical Studies (14).]* Adverse reactions which occurred in at least 10% of patients in either treatment arm and were higher in the combination arm are shown in Table 1.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (>20%) during therapy with TYKERB plus capecitabine were gastrointestinal (diarrhea, nausea, and vomiting), dermatologic (palmar-plantar erythrodysesthesia and rash), and fatigue. Diarrhea was the most common adverse reaction resulting in discontinuation of study medication.

The most common grade 3 and 4 adverse reactions (NCI CTC v3) were diarrhea and palmar-plantar erythrodysesthesia. Selected laboratory abnormalities are shown in Table 2.

Table 1. Adverse Reactions Occurring in ≥10% of Patients

	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m²/day (N = 198)			Capecitabine 2,500 mg/m²/day (N = 191)		
Reactions	**All Grades* %**	**Grade 3 %**	**Grade 4 %**	**All Grades* %**	**Grade 3 %**	**Grade 4 %**
Gastrointestinal disorders						
Diarrhea	65	13	1	40	10	0
Nausea	44	2	0	43	2	0
Vomiting	26	2	0	21	2	0
Stomatitis	14	0	0	11	<1	0
Dyspepsia	11	<1	0	3	0	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia	53	12	0	51	14	0
Rash†	28	2	0	14	1	0
Dry skin	10	0	0	6	0	0
General disorders and administrative site conditions						
Mucosal inflammation	15	0	0	12	2	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	12	1	0	7	<1	0
Back pain	11	1	0	6	<1	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	12	3	0	8	2	0
Psychiatric disorders						
Insomnia	10	<1	0	6	0	0

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

† Grade 3 dermatitis acneiform was reported in <1% of patients in TYKERB plus capecitabine group.

Table 2. Selected Laboratory Abnormalities

Parameters	TYKERB 1,250 mg/m²/day + Capecitabine 2,000 mg/m²/day			Capecitabine 2,500 mg/m²/day		
	All Grades* %	Grade 3 %	Grade 4 %	All Grades* %	Grade 3 %	Grade 4 %
Hematologic						
Hemoglobin	56	<1	0	53	1	0
Platelets	18	<1	0	17	<1	<1
Neutrophils	22	3	<1	31	2	1
Hepatic						
Total Bilirubin	45	4	0	30	3	0
AST	49	2	<1	43	2	0
ALT	37	2	0	33	1	0

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Decreases in Left Ventricular Ejection Fraction: Due to potential cardiac toxicity with HER2 (ErbB2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week intervals. LVEF decreases were defined as signs or symptoms of deterioration in left ventricular cardiac function that are ≥ Grade 3 (NCI CTCAE), or a ≥20% decrease in left ventricular cardiac ejection fraction relative to baseline which is below the institution's lower limit of normal. Among 198 patients who patients received lapatinib/capecitabine combination treatment, 3 experienced grade 2 and one had grade 3 LVEF adverse reactions (NCI CTC 3.0). *[See Warnings and Precautions (5.1).]*

7 DRUG INTERACTIONS

7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport Systems

Lapatinib inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8. Lapatinib did not significantly inhibit the following enzymes in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or UGT enzymes in vitro, however, the clinical significance is unknown.

Lapatinib inhibits human P-glycoprotein. If TYKERB is administered with drugs that are substrates of Pgp, increased concentrations of the substrate drug are likely, and caution should be exercised.

7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

Lapatinib undergoes extensive metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 alter lapatinib concentrations significantly *(see Ketoconazole and Carbamazepine sections, below)*. Dose adjustment of lapatinib should be

considered for patients who must receive concomitant strong inhibitors or concomitant strong inducers of CYP3A4 enzymes *[see Dosage and Administration (2.2)]*.

Ketoconazole: In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

Carbamazepine: In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to lapatinib was decreased approximately 72%.

7.3 Drugs that Inhibit Drug Transport Systems

Lapatinib is a substrate of the efflux transporter P-glycoprotein (Pgp, ABCB1). If TYKERB is administered with drugs that inhibit Pgp, increased concentrations of lapatinib are likely, and caution should be exercised.

7.4 Other Chemotherapy Agents

In a separate study, concomitant administration of lapatinib with capecitabine did not meaningfully alter the pharmacokinetics of either agent (or the metabolites of capecitabine).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.5)].

8.3 Nursing Mothers

It is not known whether lapatinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TYKERB, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of TYKERB in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were 75 years of age and older. No overall differences in safety or effectiveness of the combination of TYKERB and capecitabine were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Lapatinib pharmacokinetics have not been specifically studied in patients with renal impairment or in patients undergoing hemodialysis. There is no experience with TYKERB in patients with severe renal impairment. However, renal impairment is unlikely to affect the pharmacokinetics of lapatinib given that less than 2% (lapatinib and metabolites) of an administered dose is eliminated by the kidneys.

8.7 Hepatic Impairment

The pharmacokinetics of lapatinib were examined in subjects with moderate (n = 8) or severe (n = 4) hepatic impairment (Child-Pugh Class B/C, respectively) and in 8 healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100 mg-dose increased approximately 14% and 63% in subjects with moderate and severe hepatic impairment, respectively. Administration of TYKERB in patients with severe hepatic impairment should be undertaken with caution due to increased exposure to the drug. A dose reduction should be considered for patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*.

10 OVERDOSAGE

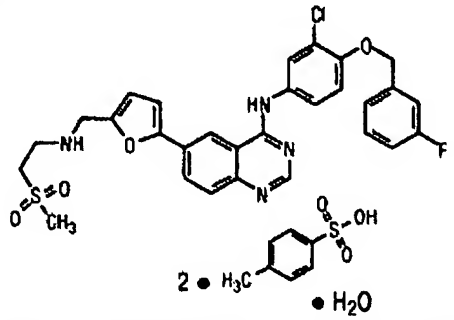
There is no known antidote for overdoses of TYKERB. The maximum oral doses of lapatinib that have been administered in clinical trials are 1,800 mg once daily. More frequent ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical trials and could result in increased toxicity. Therefore, missed doses should not be replaced and dosing should resume with the next scheduled daily dose.

There has been a report of one patient who took 3,000 mg of TYKERB for 10 days. This patient had grade 3 diarrhea and vomiting on Day 10. The event resolved following IV hydration and interruption of treatment with TYKERB and letrozole.

Because lapatinib is not significantly renally excreted and is highly bound to plasma proteins, hemodialysis would not be expected to be an effective method to enhance the elimination of lapatinib.

11 DESCRIPTION

Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase inhibitors. It is present as the monohydrate of the ditosylate salt, with chemical name *N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-methylbenzenesulfonate) monohydrate. It has the molecular formula $C_{29}H_{26}ClFN_4O_4S$ $(C_7H_8O_3S)_2$ H_2O and a molecular weight of 943.5. Lapatinib ditosylate monohydrate has the following chemical structure:



Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is 0.001 mg/mL at 25°C.

Each 250 mg tablet of TYKERB contains 405 mg of lapatinib ditosylate monohydrate, equivalent to 398 mg of lapatinib ditosylate or 250 mg lapatinib free base.

The inactive ingredients of TYKERB are: **Tablet Core**: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. **Coating**: Orange film-coat: FD&C yellow No. 6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400, polysorbate 80, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lapatinib is a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domains of both Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal Receptor Type 2 (HER-2 [ErbB2]) receptors (estimated K_i^{app} values of 3nM and 13nM, respectively) with a dissociation half-life of ≥300 minutes. Lapatinib inhibits ErbB-driven tumor cell growth in vitro and in various animal models.

An additive effect was demonstrated in an in vitro study when lapatinib and 5-FU (the active metabolite of capecitabine) were used in combination in the 4 tumor cell lines tested. The growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib retained significant activity against breast cancer cell lines selected for long-term growth in trastuzumab-containing medium in vitro. These in vitro findings suggest non-cross-resistance between these two agents.

12.3 Pharmacokinetics

Absorption: Absorption following oral administration of TYKERB is incomplete and variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to 1.5 hour). Peak plasma concentrations (C_{max}) of lapatinib are achieved approximately 4 hours after administration. Daily dosing of TYKERB results in achievement of steady state within 6 to 7 days, indicating an effective half-life of 24 hours.

At the dose of 1,250 mg daily, steady state geometric mean (95% confidence interval) values of C_{max} were 2.43 mcg/mL (1.57 to 3.77 mcg/mL) and AUC were 36.2 mcg.hr/mL (23.4 to 56 mcg.hr/mL).

Divided daily doses of TYKERB resulted in approximately 2-fold higher exposure at steady state (steady state AUC) compared to the same total dose administered once daily.

Systemic exposure to lapatinib is increased when administered with food. Lapatinib AUC values were approximately 3- and 4-fold higher (C_{max} approximately 2.5- and 3-fold higher) when administered with a low fat (5% fat-500 calories) or with a high fat (50% fat-1,000 calories) meal, respectively.

Distribution: Lapatinib is highly bound (>99%) to albumin and alpha-1 acid glycoprotein. In vitro studies indicate that lapatinib is a substrate for the transporters breast cancer resistance protein (BCRP, ABCG2) and P-glycoprotein (Pgp, ABCB1). Lapatinib has also been shown in vitro to inhibit these efflux transporters, as well as the hepatic uptake transporter OATP 1B1, at clinically relevant concentrations.

Metabolism: Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated metabolites, none of which accounts for more than 14% of the dose recovered in the feces or 10% of lapatinib concentration in plasma.

Elimination: At clinical doses, the terminal phase half-life following a single dose was 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of 27% (range 3 to 67%) of an oral dose.

Effects of Age, Gender, or Race: Studies of the effects of age, gender, or race on the pharmacokinetics of lapatinib have not been performed.

12.4 QT Prolongation

The QT prolongation potential of lapatinib was assessed as part of an uncontrolled, open-label dose escalation study in advanced cancer patients. Eighty-one patients received daily doses of lapatinib ranging from 175 mg/day to 1,800 mg/day. Serial ECGs were collected on Day 1 and Day 14 to evaluate the effect of lapatinib on QT intervals. Thirteen of the 81 subjects were found to have either QTcF (corrected QT by the Friedericia method) >480 msec or an increase in QTcF >60 msec by automated machine-read evaluation of ECG. Analysis of the data suggested a relationship between lapatinib concentration and the QTc interval.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies with lapatinib are ongoing.

Lapatinib was not clastogenic or mutagenic in the Chinese hamster ovary chromosome aberration assay, microbial mutagenesis (Ames) assay, human lymphocyte chromosome aberration assay or the in vivo rat bone marrow chromosome aberration assay at single doses up to 2,000 mg/kg. However, an impurity in the drug product (up to 4 ppm or 8 mcg/day) was genotoxic when tested alone in both in vitro and in vivo assays.

There were no effects on male or female rat mating or fertility at doses up to 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times the expected human clinical exposure based on AUC, respectively). The effect of lapatinib on human fertility is unknown. However, when female rats were given oral doses of lapatinib during breeding and through the first 6 days of gestation, a significant decrease in the number of live fetuses was seen at 120 mg/kg/day and in the fetal body weights at ≥60 mg/kg/day (approximately 6.4 times and 3.3 times the expected human clinical exposure based on AUC, respectively).

14 CLINICAL STUDIES

The efficacy and safety of TYKERB in combination with capecitabine in breast cancer were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2 (ErbB2) over-expressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic

breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab.

Patients were randomized to receive either TYKERB 1,250 mg once daily (continuously) plus capecitabine 2,000 mg/m^2/day on Days 1-14 every 21 days, or to receive capecitabine alone at a dose of 2,500 mg/m^2/day on Days 1-14 every 21 days. The endpoint was time to progression (TTP). TTP was defined as time from randomization to tumor progression or death related to breast cancer. Based on the results of a pre-specified interim analysis, further enrollment was discontinued. Three hundred and ninety-nine (399) patients were enrolled in this study. The median age was 53 years and 14% were older than 65 years. Ninety-one percent (91%) were Caucasian. Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes, and trastuzumab.

Efficacy analyses four months after the interim analysis are presented in Table 3, Figure 1, and Figure 2.

Table 3. Efficacy Results

	Independent Assessment*		**Investigator Assessment**	
	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m^2/day	**Capecitabine 2,500 mg/m^2/day**	**TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m^2/day**	**Capecitabine 2,500 mg/m^2/day**
	(N = 198)	**(N = 201)**	**(N = 198)**	**(N = 201)**
Number of TTP events	82	102	121	126
Median TTP, weeks (25th, 75th, Percentile), weeks	27.1 (17.4, 49.4)	18.6 (9.1, 36.9)	23.9 (12.0, 44.0)	18.3 (6.9, 35.7)
Hazard Ratio (95% CI) p value	0.57 (0.43, 0.77) 0.00013		0.72 (0.56, 0.92) 0.00762	
Response Rate (%) (95% CI)	23.7 (18.0, 30.3)	13.9 (9.5, 19.5)	31.8 (25.4, 38.8)	17.4 (12.4, 23.4)

TTP = Time to progression.

* The time from last tumor assessment to the data cut-off date was >100 days in approximately 30% of patients in the independent assessment. The pre-specified assessment interval was 42 or 84 days.

Figure 1. Kaplan-Meier Estimates for Independent Review Panel-evaluated Time to Progression

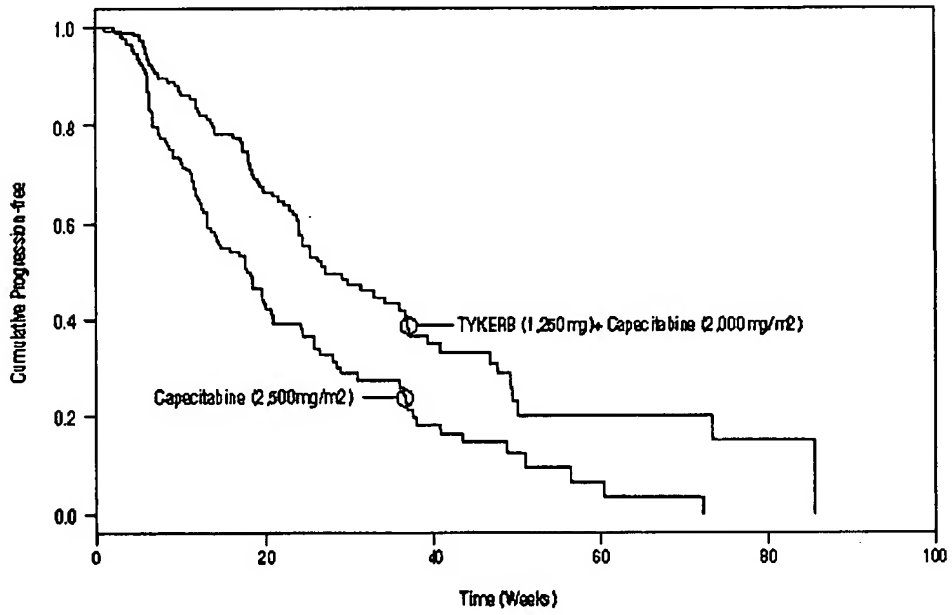
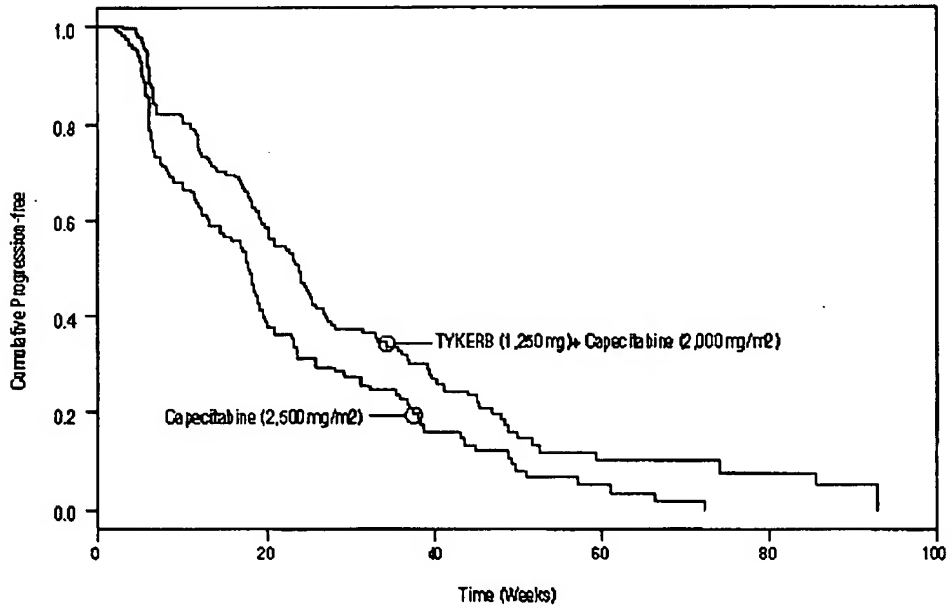


Figure 2. Kaplan-Meier Estimates for Investigator Assessment Time to Progression



At the time of updated analysis, 30% of patients had died and the data for survival analysis are not mature. Fifty-five patients (28%) in the TYKERB plus capecitabine group and 64 subjects (32%) in the capecitabine group had died.

16 HOW SUPPLIED/STORAGE AND HANDLING

The 250 mg tablets of TYKERB are oval, biconvex, orange, and film-coated with GS XJG debossed on one side and are available in:

Bottles of 150 tablets: NDC 0173-0752-00

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (17.6)

17.1 Decreased Left Ventricular Ejection Fraction

Patients should be informed that TYKERB has been reported to decrease left ventricular ejection fraction which may result in shortness of breath, palpitations, and/or fatigue. Patients should inform their physician if they develop these symptoms while taking TYKERB.

17.2 Diarrhea

Patients should be informed that TYKERB often causes diarrhea which may be severe in some cases. Patients should be told how to manage and/or prevent diarrhea and to inform their physician if severe diarrhea occurs during treatment with TYKERB.

17.3 Drug Interactions

TYKERB may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products.

17.4 Food

Patients should be informed of the importance of taking TYKERB at least one hour before or one hour after a meal, in contrast to capecitabine which should be taken with food or within 30 minutes after food.

17.5 Divided Dosing

The dose of TYKERB should not be divided. Patients should be advised of the importance of taking TYKERB once daily, in contrast to capecitabine which is taken twice daily.

17.6 FDA Approved Patient Labeling

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

17.6 FDA-Approved Patient Labeling

PATIENT INFORMATION

TYKERB® (TIE-curb)
(lapatinib) tablets

Read this leaflet before you start taking TYKERB and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

What is TYKERB?

TYKERB is used with the medicine capecitabine for the treatment of patients with advanced or metastatic breast cancer that is HER2 positive, and who have already had certain other breast cancer treatments.

Before you start taking TYKERB, tell your doctor about all of your medical conditions, including if you:

- have heart problems.
- have liver problems. You may need a lower dose of TYKERB.
- are pregnant or may become pregnant. TYKERB may harm an unborn baby. If you become pregnant during treatment with TYKERB, tell your doctor as soon as possible.
- are breastfeeding. It is not known if TYKERB passes into your breast milk or if it can harm your baby. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines and herbal and dietary supplements. TYKERB and many other medicines may interact with each other. Your doctor needs to know what medicines you take so he or she can choose the right dose of TYKERB for you.

Especially tell your doctor if you take:

- antibiotics and anti-fungals (drugs used to treat infections)
- HIV (AIDS) treatments
- anticonvulsant drugs (drugs used to treat seizures)
- calcium channel blockers (drugs used to treat certain heart disorders or high blood pressure)
- antidepressants
- drugs used for stomach ulcers

- St. John's Wort or other herbal supplements

Know the medicines you take. Keep a list of your medicines with you to show your doctor. Do not take other medicines during treatment with TYKERB without first checking with your doctor.

Because TYKERB is given with another drug called capecitabine, you should also discuss with your doctor or pharmacist any medicines that should be avoided when taking capecitabine.

How should I take TYKERB?

- Take TYKERB exactly as your doctor has told you. TYKERB and capecitabine are taken in 21 day cycles. The usual dose of TYKERB is 1,250 mg (5 tablets) taken by mouth, **one time a day on days 1 to 21**. Your doctor will tell you the dose of capecitabine you should take and when you should take it.
- TYKERB should be taken at least one hour before, or at least one hour after food.
- Do not eat or drink grapefruit products while taking TYKERB.
- Your doctor may adjust your dose of TYKERB depending on how you tolerate the treatment.
- If you forget to take your dose of TYKERB, take it as soon as you remember that day. If you miss a day, do not double your dose the next day. Just skip the missed dose.

What are the possible side effects of TYKERB?

Serious side effects include:

- **heart problems**
  - decreased pumping of blood from the heart
  - abnormal heart beat

  Call your doctor right away if you have palpitations or are short of breath.
- **severe diarrhea**, which may lead to you becoming dehydrated

Common side effects of TYKERB in combination with capecitabine include:

- diarrhea
- red, painful hands and feet
- nausea
- rash
- vomiting
- tiredness
- mouth sores
- loss of appetite
- indigestion

Tell your doctor about any side effect that gets serious or that does not go away.

These are not all the side effects with TYKERB. Ask your doctor or pharmacist for more information.

You may also get side effects from capecitabine. Talk to your doctor about possible side effects with capecitabine.

How should I store TYKERB tablets?

- Store TYKERB tablets at room temperature between 59° and 86°F (15° to 30°C). Keep the container closed tightly.
- Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.
- **Keep TYKERB and all medicines out of the reach of children.**

General information about TYKERB

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TYKERB for any other condition for which it was not prescribed. Do not give TYKERB to other people, even if they have the same condition that you have. It may harm them.

This leaflet summarizes the most important information about TYKERB. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about TYKERB that is written for health professionals. For more information you can call toll-free 1-888-825-5249.

What are the ingredients in TYKERB?

Active Ingredient: Lapatinib.

Inactive Ingredients: Tablet Core: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. **Coating**: Orange film-coat: FD&C yellow #6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400, polysorbate 80, titanium dioxide.

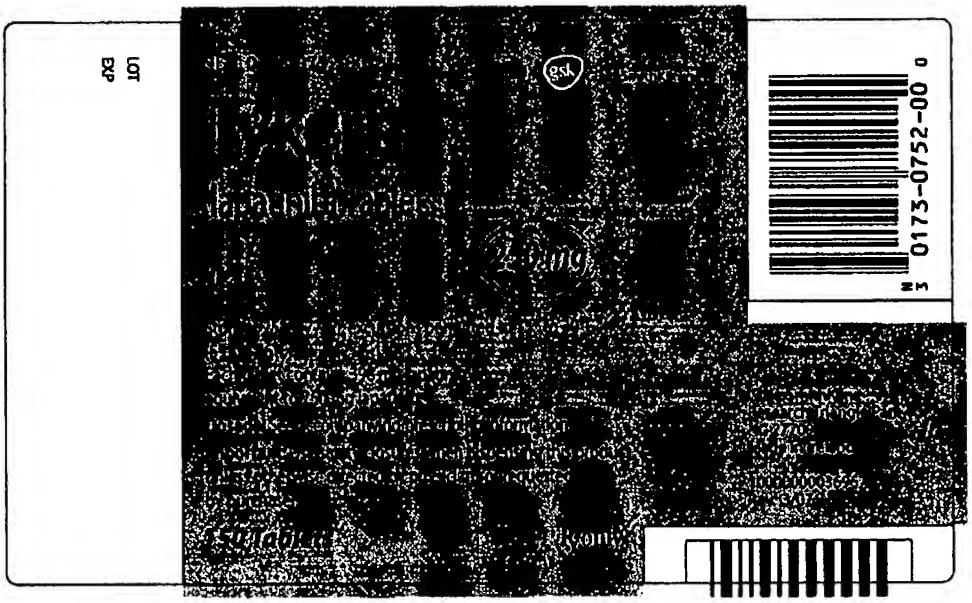
TYKERB Tablets are oval, biconvex, orange, film-coated with GS XJG printed on one side.

TYKERB is a trademark of GlaxoSmithKline.

GlaxoSmithKline
Research Triangle Park, NC 27709

TKB:1PI

Revised: March 2007



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180 mm Measuring Bar

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Richard Pazdur
3/13/2007 02:11:43 PM

EXHIBIT 7

Copy of U.S. Patent No. 6,713,485

US006713485B2

(12) **United States Patent**
Carter et al.

(10) **Patent No.: US 6,713,485 B2**
(45) **Date of Patent: Mar. 30, 2004**

(54) **HETEROCYCLIC COMPOUNDS**

(75) Inventors: **Malcolm Clive Carter**, Ware (GB); **George Stuart Cockerill**, Bedford (GB); **Stephen Barry Guntrip**, Hertford (GB); **Karen Elizabeth Lackey**, Hillsborough, NC (US); **Kathryn Jane Smith**, Hertfordshire (GB)

(73) Assignee: **SmithKline Beecham Corporation**, Philadelphia, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 49 days.

(21) Appl. No.: **10/071,358**

(22) Filed: **Feb. 8, 2002**

(65) **Prior Publication Data**

US 2002/0147205 A1 Oct. 10, 2002

Related U.S. Application Data

(63) Continuation of application No. 09/582,746, filed as application No. PCT/EP99/00048 on Jan. 8, 1999.

(30) **Foreign Application Priority Data**

Jan. 12, 1998 (GB) 9800569
Jan. 8, 1999 (WO) PCT/EP99/00048

(51) **Int. Cl.**[7] **A61K 31/517**; C07D 239/72
(52) **U.S. Cl.** **514/266.24**; 544/293
(58) **Field of Search** 514/266.24; 544/293

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Primary Examiner—Alan L. Rotman
Assistant Examiner—Tamthon N. Truong
(74) *Attorney, Agent, or Firm*—John L. Lemanowicz

(57) **ABSTRACT**

The present invention relates to substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. Specifically, the invention relates to quinazoline derivatives useful in treating disorders mediated by protein tyrosine kinase activity, in particular erbB-2 and/or EGFR activity.

18 Claims, No Drawings

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HETEROCYCLIC COMPOUNDS

This is a continuation of application Ser. No. 09/582,746, filed Jan. 30, 2000, which is a 371 of PCT/EP99/000, filed Jan. 8, 1999.

The present invention relates to a series of substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to quinoline, quinazoline, pyridopyridine and pyridopyrimidine derivatives which exhibit protein tyrosine kinase inhibition.

Protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth and differentiation (A. F. Wilks, Progress in Growth Factor Research, 1990, 2, 97–111; S. A. Courtneidge, Dev. Supp.I, 1993, 57–64; J. A. Cooper, Semin. Cell Biol., 1994, 5(6), 377–387; R. F. Paulson, Semin. Immunol., 1995, 7(4), 267–277; A. C. Chan, Curr. Opin. Immunol., 1996, 8(3), 394–401). Protein tyrosine kinases can be broadly classified as receptor (e.g. EGFr, c-erbB-2, c-met, tie-2, PDGFr, FGFr) or non-receptor (e.g. c-src, Ick, zap70) kinases. Inappropriate or uncontrolled activation of many of these kinase, i.e. aberrant protein tyrosine kinase activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth.

Aberrant activity of protein tyrosine kinases, such as c-erbB-2, c-src, c-met, EGFr and PDGFr have been implicated in human malignancies. Elevated EGFr activity has, for example, been implicated in non-small cell lung, bladder and head and neck cancers, and increased c-erbB-2 activity in breast, ovarian, gastric and pancreatic cancers. Inhibition of protein tyrosine kinases should therefore provide a treatment for tumours such as those outlined above.

Aberrant protein tyrosine kinase activity has also been implicated in a variety of other disorders: psoriasis, (Dvir et al, J. Cell. Biol; 1991, 113, 857–865), fibrosis, atherosclerosis, restenosis, (Buchdunger et al, Proc. Natl. Acad. Sci. USA; 1991, 92, 2258–2262), auto-immune disease, allergy, asthma, transplantation rejection (Klausner and Samelson, Cell; 1991, 64, 875–878), inflammation (Berkois, Blood; 1992, 79(9), 2446–2454), thrombosis (Salari et al, FEBS; 1990,263(1), 104–108) and nervous system diseases (Ohmichi et al, Biochemistry, 1992, 31, 4034–4039). Inhibitors of the specific protein tyrosine kinases involved in these diseases eg PDGF-R in restenosis and EGF-R in psoriasis, should lead to novel therapies for such disorders. P56lck and zap 70 are indicated in disease conditions in which T cells are hyperactive e.g. rheumatoid arthritis, autoimmune disease, allergy, asthma and graft rejection. The process of angiogenesis has been associated with a number of disease states (e.g. tumourogenesis, psoriasis, rheumatoid arthritis) and this has been shown to be controlled through the action of a number of receptor tyrosine kinases (L. K. Shawver, DDT, 1997, 2(2), 50–63).

It is therefore a general object of the present invention to provide compounds suitable for the treatment of disorders mediated by protein tyrosine kinase activity, and in particular treatment of the above mentioned disorders.

In addition to the treatment of tumours, the present invention envisages that other disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition, including preferential inhibition, of the appropriate protein tyrosine kinase activity.

Broad spectrum inhibition of protein tyrosine kinase may not always provide optimal treatment of, for example tumours, and could in certain cases even be detrimental to

subjects since protein tyrosine kinases provide an essential role in the normal regulation of cell growth.

It is another object of the present invention to provide compounds which preferentially inhibit protein tyrosine kinases, such as EGFr, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFr, c-src, Ick, Zap70, and fyn. There is also perceived to be a benefit in the preferential inhibition involving small groups of protein tyrosine kinases, for example groups including two or more of c-erbB-2, c-erbB-4, EGF-R, Ick and zap70.

A further object of the present invention is to provide compounds useful in the treatment of protein tyrosine kinase related diseases which minimise undesirable side-effects in the recipient.

The present invention relates to heterocyclic compounds which may be used to treat disorders mediated by protein tyrosine kinases and in particular have anti-cancer properties. More particularly, the compounds of the present invention are potent inhibitors of protein tyrosine kinases such as such as EGFr, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFr, c-src, lck, Zap70, and fyn, thereby allowing clinical management of particular diseased tissues.

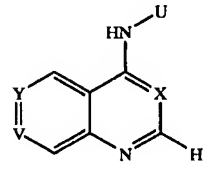
The present invention envisages, in particular, the treatment of human malignancies, for example breast, non-small cell lung, ovary, stomach, and pancreatic tumours, especially those driven by EGF-R or erbB-2, using the compounds of the present invention. For example, the invention includes compounds which are highly active against the c-erbB-2 protein tyrosine kinase often in preference to the EGF receptor kinase hence allowing treatment of c-erbB-2 driven tumours. However, the invention also includes compounds which are highly active against both c-erbB-2 and EGF-R receptor kinases hence allowing treatment of a broader range of tumours.

The present invention also includes compounds which are active against Ick and/or zap70 receptor kinases; these may also be active against c-erbB-2 and/or EGF-R receptor kinases. The compounds may be selective towards Ick and/or zap70 in comparison to c-erbB-2 and/or EGF-R.

More particularly, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity in a relatively selective manner, thereby minimising potential side effects.

Accordingly, the present invention provides a compound of formula (I)

(I)



or a salt or solvate thereof;

wherein X is N or CH;
Y is CR^1 and V is N;
or Y is N and V is CR^1;
or Y is CR^1 and V is CR^2;
or Y is CR^2 and V is CR^1;
R^1 represents a group $CH_3SO_2CH_2CH_2NHCH_2$—Ar—, wherein Ar is selected from phenyl, furan, thiophene, pyrrole and thiazole, each of which may optionally be substituted by one or two halo, C_{1-4} alkyl or C_{1-4} alkoxy groups;

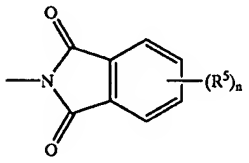
R^2 is selected from the group comprising hydrogen, halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino and di[C_{1-4} alkyl]amino;

U represents a phenyl, pyridyl, 3H-imidazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl or 1H-benzotriazolyl group, substituted by an R^3 group and optionally substituted by at least one independently selected R^4 group;

R^3 is selected from a group comprising benzyl, halo-, dihalo- and trihalobenzyl, benzoyl, pyridylmethyl, pyridylmethoxy, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl;

or R^3 represents trihalomethylbenzyl or trihalomethylbenzyloxy;

or R^3 represents a group of formula



wherein each R^5 is independently selected from halogen, C_{1-4} alkyl and C_{1-4} alkoxy; and n is 0 to 3;

each R^4 is independently hydroxy, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, carboxy, carbamoyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkanoylamino, N-(C_{1-4} alkyl)carbamoyl, N,N-di(C_{1-4} alkyl)carbamoyl, cyano, nitro and trifluoromethyl;

with the proviso that the following compounds are excluded:

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl-amine;

(4-Benzyloxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl-amine;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl-amine;

(1-Benzyl-1H-indazol-5-yl)-(7-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl-amine;

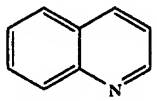
(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-1-methyl-pyrrol-2-yl)-quinazolin-4-yl-amine;

and their hydrochloride salts.

Solvates of the compounds of formula (I) are also included within the scope of the present invention.

The definitions for X, Y and V thus give rise to a number of possible basic ring systems for the compounds of formula (I). In particular the compounds may contain the following basic ring systems:

(1)



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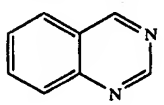

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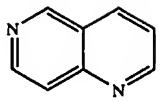

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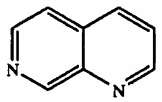

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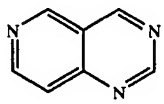
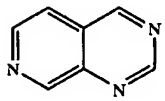


(6)



It will be seen that for compounds containing the basic ring system (1) the group R^1 may be at the 6- or 7-position; the compounds in which R^1 is in the 7-position are of particular interest in the context of Ick and/or zap70 activity.

It will be seen that for compounds containing the basic ring system (2) the group R^1 may be at the 6- or 7-position; the compounds in which R^1 is in the 6-position are of particular interest in the context of c-erbB-2 activity whereas the compounds in which R^1 is in the 7-position are of particular interest in the context of Ick and/or zap70 activity.

Ring systems (1), (2), (5) and (6) are preferred; ring systems (2) and (6) are more preferred.

Ring system (1) is also more preferred.

Alkyl groups containing three or more carbon atoms may be straight, branched or cyclised; preferably they are straight or branched. References to a specific alkyl group such as "butyl" is intended to refer to the straight chain (n-) isomer only. References to other generic terms such as alkoxy, alkylamino etc. are to be interpreted analogously.

Suitable values for the various groups listed above within the definitions for R^1, R^2, R^4 and R^5 are as follows:

halo is, for example, fluoro, chloro, bromo or iodo; preferably it is fluoro, chloro or bromo, more preferably fluoro or chloro;

C_{1-4} alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl; preferably it is methyl, ethyl, propyl, isopropyl or butyl, more preferably methyl;

C_{2-4} alkenyl is, for example, ethenyl, prop-1-enyl or prop-2-enyl; preferably it is ethenyl;

C_{2-4} alkynyl is, for example, ethynyl, prop-1-ynyl or prop-2-ynyl; preferably it is ethynyl;

C_{1-4} alkoxy is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy; preferably it is methoxy, ethoxy, propoxy, isopropoxy or butoxy; more preferably it is methoxy;

C_{1-4} alkylamino is, for example, methylamino, ethylamino or propylamino; preferably it is methylamino;

di[C_{1-4} alkyl]amino is, for example, dimethylamino, diethylamino, N-methyl-N-ethylamino or dipropylamino; preferably it is dimethylamino;

C_{1-4} alkylthio is, for example, methylthio, ethylthio, propylthio or isopropylthio, preferably methylthio;

C_{1-4} alkylsulphinyl is, for example, methylsulphinyl, ethylsulphinyl, propylsulphinyl or isopropylsulphinyl, preferably methylsulphinyl;

C_{1-4} alkylsulphonyl is, for example, methanesulphonyl, ethylsulphonyl, propylsulphonyl or isopropylsulphonyl, preferably methanesulphonyl;

C_{1-4} alkylcarbonyl is, for example methylcarbonyl, ethylcarbonyl or propylcarbonyl;

C_{1-4} alkoxycarbonyl is, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl or tert-butoxycarbonyl;

C_{1-4} alkanoylamino (where the number of carbon atoms includes the CO functionality) is, for example, formamido, acetamido, propionamido or butyramido;

N-(C_{1-4} alkyl)carbamoyl is, for example, N-methylcarbamoyl or N-ethylcarbamoyl;

N,N-di(C_{1-4} alkyl)carbamoyl is, for example, N,N-dimethylcarbamoyl, N-methyl-N-ethylcarbamoyl or N,N-diethylcarbamoyl.

In an especially preferred embodiment X is N, Y is CR^1 and V is CR^2 (ring system (2) above).

In a further especially preferred embodiment X is N, Y is CR^2 and V is CR^1 (ring system (2) above).

In a further especially preferred embodiment X is N, Y is CR^1 and V is N (ring system (6) above).

In a preferred embodiment R^2 represents hydrogen or C_{1-4} alkoxy.

In a more preferred embodiment R^2 represents hydrogen or methoxy.

In a further preferred embodiment R^2 represents halo; more preferred R^2 is fluoro.

In a preferred embodiment the group Ar is substituted by one halo, C_{1-4} alkyl or C_{1-4} alkoxy group.

In a more preferred embodiment the group Ar is substituted by a C_{1-4} alkyl group.

In a further more preferred embodiment the group Ar does not carry any optional substituents.

In a further more preferred embodiment Ar represents furan, phenyl or thiazole, each of which may optionally be substituted as indicated above.

In a further more preferred embodiment Ar represents furan or thiazole, each of which may optionally be substituted as indicated above.

In a most preferred embodiment Ar represents unsubstituted furan or thiazole.

The side chain $CH_3SO_2CH_2CH_2NHCH_2$ may be linked to any suitable position of the group Ar. Similarly, the group R^1 may be linked to the carbon atom carrying it from any suitable position of the group Ar.

In a preferred embodiment, when Ar represents furan the side chain $CH_3SO_2CH_2CH_2NHCH_2$ is in the 4-position of the furan ring and the link to the carbon atom carrying the group R^1 is from the 2-position of the furan ring.

In another preferred embodiment, when Ar represents furan the side chain $CH_3SO_2CH_2CH_2NHCH_2$ is in the 3-position of the furan ring and the link to the carbon atom carrying the group R^1 is from the 2-position of the furan ring.

In a most preferred embodiment, when Ar represents furan the side chain $CH_3SO_2CH_2CH_2NHCH_2$ is in the 5-position of the furan ring and the link to the carbon atom carrying the group R^1 is from the 2-position of the furan ring.

In a further most preferred embodiment, when Ar represents thiazole the side chain $CH_3SO_2CH_2CH_2NHCH_2$ is in the 2-position of the thiazole ring and the link to the carbon atom carrying the group R^1 is from the 4-position of the thiazole ring.

The R^3 and R^4 groups may be bound to the ring system U by either a carbon atom or a heteroatom of the ring system. The ring system itself may be bound to the bridging NH group by a carbon atom or a heteroatom but is preferably bound by a carbon atom. The R^3 and R^4 groups may be bound to either ring when U represents a bicyclic ring system, but these groups are preferably bound to the ring which is not bound to the bridging NH group in such a case.

In a preferred embodiment U represents a phenyl, indolyl, or 1H-indazolyl group substituted by an R^3 group and optionally substituted by at least one independently selected R^4 group.

In a more preferred embodiment U represents a phenyl or 1H-indazolyl group substituted by an R^3 group and optionally substituted by at least one independently selected R^4 group.

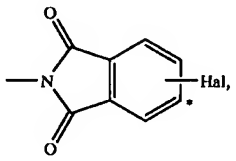
In a more preferred embodiment, where U represents a phenyl group the group R^3 is in the para- position relative to the bond from U to the linking NH group.

In a further more preferred embodiment, where U represents a 1H-indazolyl group the group R^3 is in the 1-position of the indazolyl group.

In a preferred embodiment R^3 represents benzyl, pyridylmethyl, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl.

In a further preferred embodiment R^3 represents trihalomethylbenzyloxy.

In a further preferred embodiment R^3 represents a group of formula



wherein Hal is Br or Cl, particularly Cl, more especially wherein the Hal substituent is in the position marked with a star in the ring as shown.

In a more preferred embodiment R^3 represents benzyloxy, fluorobenzyloxy (especially 3-fluorobenzyloxy), benzyl, phenoxy and benzenesulphonyl.

In a further more preferred embodiment R^3 represents bromobenzyloxy (especially 3-bromobenzyloxy) and trifluoromethylbenzyloxy.

In a further preferred embodiment the ring U is not substituted by an R^4 group; in an especially preferred embodiment U is phenyl or indazolyl unsubstituted by an R^4 group.

In a further preferred embodiment the ring U is substituted by an R^4 group selected from halo or C_{1-4} alkoxy; especially chloro, fluoro or methoxy.

In a more preferred embodiment the ring U is substituted by an R^4 group wherein R^4 represents halo, especially 3-fluoro.

In an especially preferred embodiment U together with R^4 represents methoxyphenyl, fluorophenyl, trifluoromethylphenyl or chlorophenyl.

In a more especially preferred embodiment U together with R^4 represents methoxyphenyl or fluorophenyl.

In an especially preferred embodiment the group U together with the substituent(s) R^3 and R^4 represents benzyloxyphenyl, (fluorobenzyloxy)phenyl, (benzenesulphonyl)phenyl, benzylindazolyl or phenoxyphenyl.

In a more especially preferred embodiment the group U together with the substituent(s) R^3 and R^4 represents benzyloxyphenyl, (3-fluorobenzyloxy)phenyl, (benzenesulphonyl)phenyl or benzylindazolyl.

In another more especially preferred embodiment the group U together with the substituent(s) R^3 and R^4 represents (3-bromobenzyloxy)phenyl, (3-trifluoromethylbenzyloxy)phenyl, or (3-fluorobenzyloxy)-3-methoxyphenyl.

In another more especially preferred embodiment the group U together with the substituent(s) R^3 and R^4 represents 3-fluorobenzyloxy-3-chlorophenyl, benzyloxy-3-chlorophenyl, benzyloxy-3-trifluoromethylphenyl, (benzyloxy)-3-fluorophenyl, (3-fluorobenzyloxy)-3-fluorophenyl or (3-fluorobenzyl)indazolyl.

In a most especially preferred embodiment the group U together with the substituent(s) R^3 and R^4 represents benzyloxyphenyl or (3-fluorobenzyloxy)phenyl.

In a preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is N; V is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); Y is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted phenyl, furan or thiazole; U is phenyl or indazole; R^3 is benzyl, fluorobenzyl, benzyloxy, fluorobenzyloxy, bromobenzyloxy, trifluoromethylbenzyloxy, phenoxy or benzenesulphonyl; and R^4 is not present or is halo (especially chloro or fluoro), or methoxy.

In a most preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is N; V is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); Y is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted furan or thiazole; U is phenyl; R^3 is benzyloxy, fluorobenzyloxy or benzenesulphonyl; and R^4 is not present or is halo (especially chloro or fluoro), or methoxy.

In a most preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is N; V is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); Y is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted furan or thiazole; U is indazole; R^3 is benzyl or fluorobenzyl; and R^4 is not present.

In a further more preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is N; Y is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); V is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted phenyl, furan or thiazole; U is phenyl or indazole; R^3 is benzyl, fluorobenzyl, benzyloxy, fluorobenzyloxy, bromobenzyloxy, trifluoromethylbenzyloxy, phenoxy or benzenesulphonyl; and R^4 is not present or is halo (especially chloro or fluoro), or methoxy.

In a further most preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is N; Y is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); V is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted furan or thiazole; U is phenyl; R^3 is benzyloxy, fluorobenzyloxy or benzenesulphonyl; and R^4 is not present or is halo (especially chloro or fluoro), or methoxy.

In a further most preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is N; Y is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); V is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted furan or thiazole; U is indazole; R^3 is benzyl or fluorobenzyl; and R^4 is not present.

In a most especially preferred embodiment there is provided a compound of formula(I) or a salt or solvate thereof wherein X is N, Y is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); V is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted furan or thiazole; U is phenyl; R^3 is phenoxy; and R^4 is not present.

In another more preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is N; V is N; Y is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted phenyl, furan or thiazole; U is phenyl or indazole; R^3 is benzyl, fluorobenzyl, benzyloxy, fluorobenzyloxy, bromobenzyloxy, trifluoromethylbenzyloxy, phenoxy or benzenesulphonyl; and R^4 is not present or is halo (especially chloro or fluoro), or methoxy.

In another most preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is N; V is N, Y is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted furan or thiazole; U is phenyl; R^3 is benzyloxy, fluorobenzyloxy or benzenesulphonyl; and R^4 is not present or is halo (especially chloro or fluoro), or methoxy.

In another most preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is N; V is N, Y is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted furan or thiazole; U is indazole; R^3 is benzyl or fluorobenzyl; and R^4 is not present.

In yet another preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is CH; Y is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); V is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted phenyl, furan or thiazole; U is phenyl or indazole; R^3 is benzyl, fluorobenzyl, benzyloxy, fluorobenzyloxy, bromobenzyloxy, trifluoromethylbenzyloxy, phenoxy or benzenesulphonyl; and R^4 is not present or is halo (especially chloro or fluoro), or methoxy.

In yet another most preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is CH; Y is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); V is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted furan or thiazole; U is phenyl; R^3 is benzyloxy, fluorobenzyloxy, phenoxy or benzenesulphonyl; and R^4 is not present or is halo (especially chloro or fluoro), or methoxy.

In yet another most preferred embodiment there is provided a compound of formula (I) or a salt or solvate thereof wherein X is CH; Y is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); V is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted furan or thiazole; U is indazole; R^3 is benzyl or fluorobenzyl; and R^4 is not present.

In a most especially preferred embodiment there is provided a compound of formula(I) or a salt or solvate thereof wherein X is CH, Y is CR^2, wherein R^2 is hydrogen, halo (especially fluoro) or C_{1-4} alkoxy (especially methoxy); V is CR^1 wherein R^1 is as defined above in which Ar is unsubstituted furan or thiazole; U is phenyl; R^3 is phenoxy; and R^4 is not present.

Preferred compounds of the present invention include:

4-(4-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzenesulphonyl-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

(4-(3-Fluorobenzyloxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;

N-{4-[(3-Fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-{4-[(3-Fluorobenzyl)oxy]-3-methoxyphenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-(Benzyloxy)phenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-(Benzyloxy) phenyl]-6-[4-({[2-(methanesulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-{4-[(3-Fluorobenzyl)oxy]-3-methoxyphenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-{4-[(3-Bromobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-{4-[(3-Fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-(Benzyloxy)-3-fluorophenyl]-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-(1-Benzyl-1H-indazol-5-yl)-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

6-[5-({[2-(Methanesulphonyl)ethyl]amino}methyl)-2-furyl]-N-(4-{[3-(trifluoromethyl)benzyl]oxy}phenyl)-4-quinazolinamine;

N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-{4-[(3-Bromobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-(Benzyloxy)phenyl]-6-[3-({[2-(methanesulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[1-(3-Fluorobenzyl)-1H-indazol-5-yl]-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

6-[5-({[2-(Methanesulphonyl)ethyl]amino}methyl)-2-furyl]-N-[4-(benzenesulphonyl)phenyl]-4-quinazolinamine;

6-[2-({[2-(Methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-N-[4-(benzenesulphonyl)phenyl]-4-quinazolinamine;

6-[2-({[2-(Methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-N-(4-{[3-(trifluoromethyl)benzyl]oxy}phenyl)-4-quinazolinamine

N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-(1-Benzyl-1H-indazol-5-yl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-(3-Fluoro-4-benzyloxyphenyl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-(3-Chloro-4-benzyloxyphenyl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

6-[5-({[2-(Methanesulphonyl)ethyl]amino}methyl)-2-furyl]-7-methoxy-N-(4-benzenesulphonyl)phenyl-4-quinazolinamine;

N-[4-(Benzyloxy)phenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-(1-Benzyl-1H-indazol-5-yl)-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-(Benzenesulphonyl)phenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino) methyl)-2-furyl]-4-quinazolinamine;

N-(3-Trifluoromethyl-4-benzyloxyphenyl)-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine;

and salts or solvates thereof, particularly pharmaceutically acceptable salts thereof.

Other preferred compounds of the present invention include:

(4-Phenoxyphenyl)-(7-(2-(2-methanesulphonyl) ethylaminomethyl)thiazol-4-yl)-quinolin-4-yl)amine;

(4-Phenoxyphenyl)-(7-(4-(2-methanesulphonyl) ethylaminomethyl)thiazol-5-yl)-quinolin-4-yl)amine;

(4-Phenoxyphenyl)-(7-(5-(2-(methanesulphonyl) ethylaminomethyl)furan-2-yl)-quinolin-4-yl)amine;

and salts or solvates thereof, particularly pharmaceutically acceptable salts thereof.

Other preferred compounds of the present invention include the following (in groups denoted hereafter as Lists 1 to 48):

List 1

(4-Phenoxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-(4-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-fu ran-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzenesulphonyl-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

List 2

(1-Benzyl-1H-indazol-5-yl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;

(4-(4-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-4-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;

List 3

(1-Benzyl-1H-indazol-5-yl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-5-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;

List 4

(1-Benzyl-1H-indazol-5-yl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;

List 5

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino) methyl)-thiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;

List 6

(1-Benzyl-1H-indazol-5-yl)-(6-(3-((2-methanesulphonyl-ethylamino) methyl)-phenyl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino) methyl)-phenyl)-pyrido [3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-pyrido [3,4-d]pyrimidin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

List 7

(1-Benzyl-1H-indazol-5-yl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-pyrido [3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-pyrido [3,4-d]pyrimidin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

List 8

(4-(4-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino) methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

List 9

(1-Benzyl-1H-indazol-5-yl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

List 10

(1-Benzyl-1H-indazol-5-yl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;

List 11

(1-Benzyl-1H-indazol-5-yl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(-2-(-methanesulphonyl-ethylamino)-methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino) methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;

List 12

(1-Benzyl-1H-indazol-5-yl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino) methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;

List 13

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;

List 14

(1-Benzyl-1H-indazol-5-yl)-(6-(3-((2-methanesulphonyl-ethylamino) methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino) methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;

List 15

(1-Benzyl-1H-indazol-5-yl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;

List 16

(4-(4-Fluorobenzyloxy)-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino) methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

List 17

(1-Benzyl-1H-indazol-5-yl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino) methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

(4-Benzenesulphonyl-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino) methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

List 18

(1-Benzyl-1H-indazol-5-yl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;

List 19

(1-Benzyl-1H-indazol-5-yl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino) methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;

List 20

(1-Benzyl-1H-indazol-5-yl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;

List 21

(1-Benzyl-1H-indazol-5-yl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-1-2-yl)-quinazolin-4-yl)-amine;

List 22

(1-Benzyl-1H-indazol-5-yl)-(7-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino) methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;

List 23

(1-Benzyl-1H-indazol-5-yl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinazolin-4-yl)-amine;

List 24

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;

(4-Benzenesulphonyl-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-((2-methanesulphonyl-ethyl amino) methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;

List 25

(1-Benzyl-1H-indazol-5-yl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;

List 26

(1-Benzyl-1H-indazol-5-yl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-4-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;

List 27

(1-Benzyl-1H-indazol-5-yl)-(6-(2-((2-methanesulphonyl-ethylamino) methyl)-thiazol-5-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-5-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;

List 28

(1-Benzyl-1H-indazol-5-yl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl i-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;

List 29

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-y)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino) methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-pyrido[3,4-d]pyridin-4-yl)-amine;

List 30

(1-Benzyl-1H-indazol-5-yl)-(6-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;

List 31

(1-Benzyl-1H-indazol-5-yl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d]pyridin-4-yl)-amine;

List 32

(4-Phenoxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinolin-4-yl)-amine;

List 33

(1-Benzyl-1H-indazol-5-yl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(5((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;

List 34

(1-Benzyl-1H-indazol-5-yl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino) methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino) methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;

List 35

(1-Benzyl-1H-indazol-5-yl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-4-yl)-quinolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinolin-4-yl)-amine;

List 36

(1-Benzyl-1H-indazol-5-yl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino) methyl)-thiazol-5-yl)-quinolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-5-yl)-quinolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino) methyl)-thiazol-5-yl)-quinolin-4-yl)-amine;

List 37

(1-Benzyl-1H-indazol-5-yl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;

List 38

(1-Benzyl-1H-indazol-5-yl)-(7-(5-((2-methanesulphonyl-ethylamino) methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;

(4-Benzenesulphonyl-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;

List 39

(1-Benzyl-1H-indazol-5-yl)-(7-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinolin-4-yl)-amine;

List 40

(1-Benzyl-1H-indazol-5-yl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinolin-4-yl)-amine;
(4-(4-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinolin-4-yl)-amine;
(4-(3-Fluorobenzyloxy)-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinolin-4-yl)-amine;
(4-Benzenesulphonyl-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinolin-4-yl)-amine;
(4-Benzyloxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-quinolin-4-yl)-amine;

List 41

(4-Benzyloxy-3-chlorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino) methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-trifluoromethylphenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-bromophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy-3-bromophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-iodophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy-3-iodophenyl)-(6-(5-((2-methanesulphonyl-ethylamino) methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-fluorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy-3-fluorophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

List 42

(4-Benzyloxy-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-trifluoromethylphenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl)-(6-(2-((2-methanesulphonyl-ethylamino) methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-iodophenyl)-(6(2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy-3-iodophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxy-3-fluorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino) methyl)-thiazol-4-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy-3-fluorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino) methyl)-thiazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

List 43

(4-Benzyloxy-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine
(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-3-trifluoromethylphenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy-3-bromophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-Benzyloxy-3-iodophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-(3-Fluoro-benzyloxy-3-iodophenyl)-(6-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;

List 44

(4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-3-bromophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

(4-(3-Fluoro-benzyloxy-3-bromophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

(4-Benzyloxy-3-iodophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;

(4-(3-Fluoro-benzyloxy-3-iodophenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine.

List 45

N-[4-(Benzyloxy)-3-chlorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-Benzyloxy-3-trifluoromethylphenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-Benzyloxy-3-bromophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy-3-bromophenyl]-7-methoxy-6-[5-(I[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-Benzyloxy-3-iodophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy-3-iodophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-Benzyloxy-3-fluorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy-3-fluorophenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[1-(3-Fluorobenzyl-1H-indazol-5-yl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

List 46

N-[4-(Benzyloxy)-3-chlorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

N-[4-Benzyloxy-3-trifluoromethylphenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

N-[4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

N-[4-Benzyloxy-3-bromophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

N-[4-(3-Fluoro-benzyloxy-3-bromophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

N-[4-Benzyloxy-3-iodophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

N-[4-(3-Fluoro-benzyloxy-3-iodophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

N-[4-Benzyloxy-3-fluorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

N-[4-(3-Fluoro-benzyloxy-3-fluorophenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

N-[1-(3-fluorobenzyl-1H-indazol-5-yl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

List 47

N-[4-(benzyloxy)-3-chlorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-Benzyloxy-3-trifluoromethylphenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4yl]-4-quinazolinamine;

N-[4-Benzyloxy-3-bromophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy-3-bromophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-Benzyloxy-3-iodophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy-3-iodophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-Benzyloxy-3-fluorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy-3-fluorophenyl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[1-(3-fluorobenzyl-1H-indazol-5-yl]-7-methoxy-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

List 48

N-[4-(benzyloxy)-3-chlorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-Benzyloxy-3-trifluoromethylphenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-bromophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy-3-bromophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-iodophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-(3-Fluoro-benzyloxy-3-iodophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[4-Benzyloxy-3-fluorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine; 2 N-[4-(3-Fluoro-benzyloxy-3-fluorophenyl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-[1-(3-fluorobenzyl-1H-indazol-5-yl]-7-fluoro-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Particularly preferred compounds of the present invention include:

(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(4-Benzyloxyphenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
N-{4-[(3-Fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[4-(Benzyloxy) phenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-(1-Benzyl-1H-indazol-5-yl)-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-[1-(3-Fluorobenzyl)-1H-indazol-5-yl]-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
6-[5-({[2-(Methanesulphonyl)ethyl]amino}methyl)-2-furyl]-N-[4-(benzenesulphonyl)phenyl]-4-quinazolinamine;
N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-(1-Benzyl-1H-indazol-5-yl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine;
N-(3-Fluoro-4-benzyloxyphenyl)-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine;
N-(3-Chloro-4-benzyloxyphenyl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine;
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-(1-Benzyl-1H-indazol-5-yl)-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine;
N-(3-Trifluoromethyl-4-benzyloxyphenyl)-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Further particularly preferred compounds of the present invention include:

(4-Phenoxyphenyl)-(7-(2-(2-methanesulphonyl) ethylaminomethyl)thiazol-4-yl)-quinolin-4-yl)amine;
(4-Phenoxyphenyl)-(7-(4-(2-methanesulphonyl) ethylaminomethyl)thiazol-5-yl)-quinolin-4-yl)amine;
(4-Phenoxyphenyl)-(7-(5-(2-(methanesulphonyl) ethylaminomethyl)furan-2-yl)-quinolin-4-yl)amine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Other particularly preferred compounds of the present invention include:

(4-Phenoxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinazolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(3-((2-methanesulphonyl-ethylamino) methyl)-phenyl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-phenyl)-quinolin-4-yl)-amine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Other most particularly preferred compounds of the present invention include:

(4-Phenoxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-4-yl)-quinolin-4-yl)-amine;

(4-Phenoxy-phenyl)-(7-(2-((2-methanesulphonyl-ethylamino)methyl)-thiazol-5-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(4-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
(4-Phenoxy-phenyl)-(7-(5-((2-methanesulphonyl-ethylamino)methyl)-thiazol-2-yl)-quinolin-4-yl)-amine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

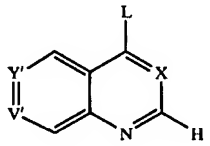
Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen in the compound of formula (I). The therapeutic activity resides in the moiety derived from the compound of the invention as defined herein and the identity of the other component is of less importance although for therapeutic and prophylactic purposes it is, preferably, pharmaceutically acceptable to the patient. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic, acids.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

(a) the reaction of a compound of formula (II)

(II)

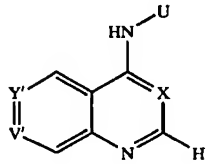


wherein X is as defined above;
Y' is CL' and V' is N;
or Y' is N and V' is CL';
or Y' is CL' and V' is CR^2;
or Y' is CR^2 and V' is CL';
wherein R^2 is as defined above, and L and L' are suitable leaving groups, with a compound of formula (III)

UNH_2 (III)

wherein U is as defined above, to prepare a compound of formula (IV)

(IV)

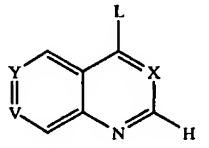


and subsequently (b) reaction with appropriate reagent(s) to substitute the group R^1 by replacement of the leaving group L'; and, if desired, (c) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

Alternatively, the compound of formula (II) as defined above is reacted with the appropriate reagents to substitute the group R^1 by replacement of the leaving group L' and then the product thereby obtained (of formula (V) below) is reacted with the compound of formula (III) as defined above, followed, if desired, by conversion of the compound of formula (I) thereby obtained into another compound of formula (I).

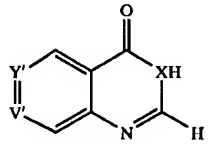
In a variant of this alternative the compound of formula (V)

(V)



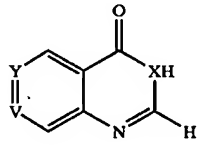
wherein X, Y, V, U and L are as defined above, may be prepared by the reaction of a compound of formula (VI)

(VI)



wherein V' and Y' are as defined above, with appropriate reagents to substitute the group R^1 for the leaving group L' to prepare a compound of formula (VII)

(VII)



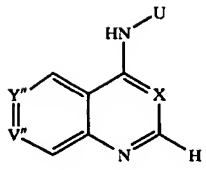
and subsequent reaction to incorporate the leaving group L. For example, a chloro leaving group can be incorporated by reaction of a corresponding 3,4-dihydropyrimidone with carbon tetrachloride/triphenylphosphine in an appropriate solvent.

The group R^1 may, therefore, be substituted onto the basic ring system by replacement of a suitable leaving group. This may, for example, be carried out by reaction of the corresponding aryl or heteroaryl stannane derivative with the corresponding compound of formula (IV) carrying the leaving group L' in the appropriate position on the ring.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

(a) reacting a compound of formula (IV) as defined above with appropriate reagent(s) to prepare a compound of formula (VIII)

(VIII)



wherein X and U are as defined above;
Y" is CT and V" is N;
or Y" is N and V" is CT;
or Y" is CT and V" is CR^2;
or Y" is CR^2 and V" is CT; wherein R^2 is as defined above and T is an appropriately functionalised group;
and (b) subsequently converting the group T into the group R^1 by means of appropriate reagent(s); and, if desired, (c) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

In one alternative, the group T would represent a group Ar as defined above carrying a formyl group (CHO).

Where T represents a group Ar carrying a formyl group the compound (of formula (VIIIa)) may be suitably prepared from the corresponding dioxolanyl substituted compound (of formula (VIIIb)), for example by acid hydrolysis. The dioxolanyl substituted compound may be prepared by reaction of a compound of formula (IV) with an appropriate reagent to substitute the relevant leaving group with the substituent carrying the dioxolanyl ring. This reagent could, for example, be an appropriate heteroaryl stannane derivative.

Therefore a suitable process may comprise reaction of a compound of formula (VIIIa) in which T is a group Ar carrying a formyl substituent (i.e. a —CHO group) with a compound of formula $CH_3SO_2CH_2CH_2NH_2$. The reaction preferably involves a reductive amination by means of an appropriate reducing agent, for example sodium triacetoxyborohydride.

Alternatively, another suitable process may comprise oxidation of a compound of formula (VIIIc) in which T is a group Ar carrying a substituent of formula $CH_3SCH_2CH_2NHCH_2$ or $CH_3SOCH_2CH_2NHCH_2$. Suitable methods for the oxidation to the desired compound of formula (I) will be well known to the person skilled in the art but include, for example, reaction with an organic peroxide, such as peracetic acid or metachlorobenzoic acid, or reaction with an inorganic oxidising agent, such as OXONE®. The compound of formula (VIIIc) in which T is a group Ar carrying a substituent of formula $CH_3SCH_2CH_2NHCH_2$ or $CH_3SOCH_2CH_2NHCH_2$ may be prepared by an analogous reaction to that described above, namely reaction of a compound of formula (VIIIa) in which T is a group Ar carrying a formyl substituent (i.e. a —CHO group) with a compound of formula $CH_3SCH_2CH_2NH_2$ or $CH_3SOCH_2CH_2NH_2$ respectively.

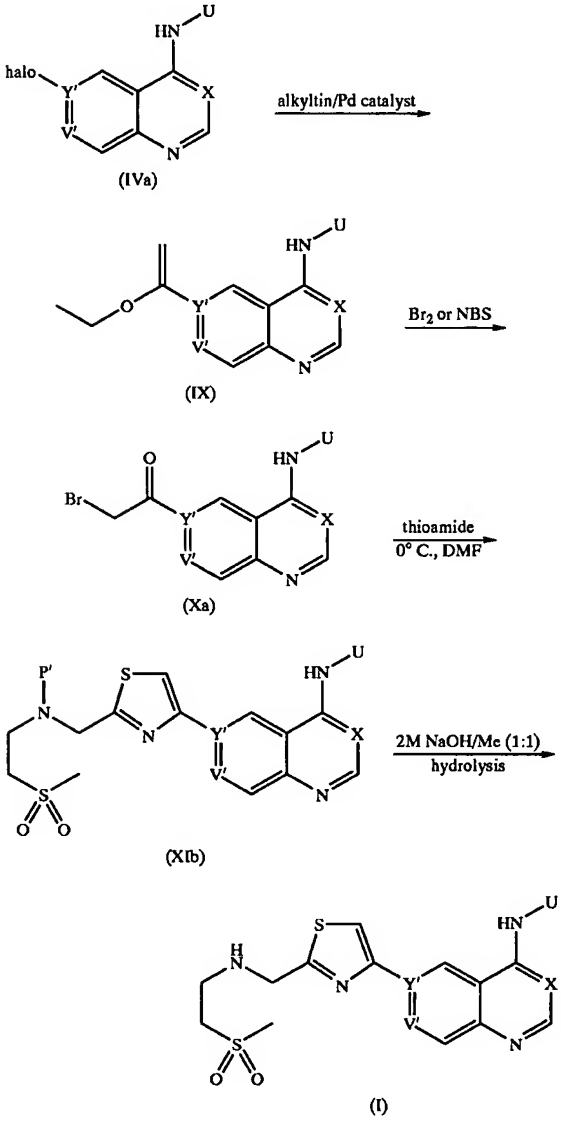
Alternatively, an analogous scheme to those described above could be used wherein the substitution of the group R^1 onto the basic ring system occurs prior to the coupling reaction with the compound of formula (III).

According to a further alternative process the group T is converted into the group R^1 by a de novo synthesis of a substituted heterocyclic system using appropriate agents. Such a process would involve standard synthetic methodology known to the person skilled in the art for building up the heterocylic ring system.

For example, T could represent a haloketone group as shown in the compound of formula (IX) in scheme 1 below which, when coupled with an appropriate N-protected thioamide [compound of formula (XI) in scheme 2], would result in the formation of an N-protected amino-substituted thiazole system of formula (X).

Scheme 1 outlines, for example, the synthesis of derivatives carrying a substituted thiazole ring as an R^1 substituent:

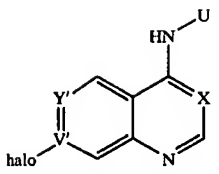
Scheme 1



wherein halo is as previously defined (preferably iodo), and P' in the compound of formula (XI) is a suitable protecting group, such as trifluorocarbonyl.

An analogous process may be used to prepare compounds of formula(I) which carry R^1 in the 7-position of the basic ring system from a starting compound of formula(IVb)

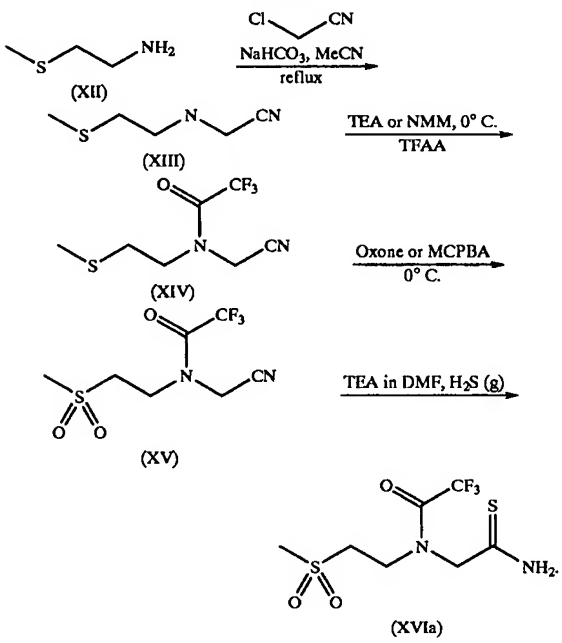
(IVb)



via intermediates of formulae (Xb) and (XIb) which are respectively analogous to those of formulae (Xa) and (XIb).

An appropriately substituted thioamide coupling reagent, suitable for preparation of a thiazole ring system, may be prepared according to Scheme 2:

Scheme 2



Wherein in scheme 2 the trifluorocarbonyl protecting group in the compounds of formula (XIV), (XV) and (XVIa) is equivalent to the group P' in scheme 1.

Alternatively, an analogous scheme to those described above could be used wherein the substitution of the group R^1 onto the basic ring system occurs prior to the coupling reaction with the compound of formula(III).

Other substituted thioamides are prepared using analogous processes to that shown above.

In general, the group R^2 will be present as a substituent in the basic ring system prior to the introduction of the group R^1 or the group NHU. Where R^2 is other than hydrogen it may in certain circumstances be necessary to protect the group prior to performing the reaction steps to introduce the R^1 and NHU substituents. Particular mention should be made of the situation where R^2 is hydroxy; suitable protecting groups to ensure non-interference with the subsequent reaction steps include the 2methoxyethoxymethyl ether (MEM) group or a bulky silyl protecting group such as tert-butyldiphenylsilyl (TBDPS).

Suitable protecting groups, methods for their introduction and methods for their removal would be well known to the person skilled in the art. For a description of protecting groups and their use see T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd edn., John Wiley & Sons, New York, 1991.

Suitable leaving groups for L and L' will be well known to those skilled in the art and include, for example, halo such as fluoro, chloro, bromo and iodo; sulphonyloxy groups such as methanesulphonyloxy and toluene-p-sulphonyloxy; alkoxy groups; and triflate.

The coupling reaction referred to above with the compound of formula (III) is conveniently carried out in the presence of a suitable inert solvent, for example a C_{1-4} alkanol, such as isopropanol, a halogenated hydrocarbon, an ether, an aromatic hydrocarbon or a dipolar aprotic solvent such as acetone, acetonitrile or DMSO at a non-extreme temperature, for example from 0 to 150° C., suitably 10 to 120° C., preferably 50 to 100° C.

Optionally, the reaction is carried out in the presence of a base. Examples of suitable bases include an organic amine such as triethylamine, or an alkaline earth metal carbonate, hydride or hydroxide, such as sodium or potassium carbonate, hydride or hydroxide.

The compound of formula (I) may be obtained from this process in the form of a salt with the acid HL, wherein L is as hereinbefore defined, or as the free base by treating the salt with a base as hereinbefore defined.

The compounds of formulae (II) and (III) as defined above, the reagents to substitute the group R^1, and the reagent(s) to convert the group T into the group R^1 are either readily available or can be readily synthesised by those skilled in the art using conventional methods of organic synthesis.

As indicated above, the compound of formula (I) prepared may be converted to another compound of formula (I) by chemical transformation of the appropriate substituent or substituents using appropriate chemical methods (see for example, J. March "Advanced Organic Chemistry", Edition III, Wiley Interscience, 1985).

For example, a compound containing an alkylthio group may be oxidised to the corresponding sulphinyl or sulphonyl compound by use of an organic peroxide (e.g. benzoyl peroxide) or suitable inorganic oxidant (eg OXONE®).

A compound containing a nitro substituent may be reduced to the corresponding amino-compound, e.g. by use of hydrogen and an appropriate catalyst (if there are no other susceptible groups), by use of Raney Nickel and hydrazine hydrate or by use of iron/acetic acid.

Amino substituents may be acylated by use of an acid chloride or an anhydride under appropriate conditions. Equally an amide group may be cleaved to the amino compound by treatment with, for example, dilute aqueous base.

An amino substituent may also be converted to a dimethylamino substituent by reaction with formic acid and sodium cyanoborohydride. Similarly, reaction of a primary or secondary amino group with another suitable aldehyde under reducing conditions will lead to the corresponding substituted amine.

All of the above-mentioned chemical transformations may also be used to convert any relevant intermediate compound to another intermediate compound prior to the final reaction to prepare a compound of formula (I); this would thus include their use to convert one compound of formula (III) to a further compound of formula (III) prior to any subsequent reaction.

Various intermediate compounds used in the above-mentioned processes, including but not limited to certain of the compounds of formulae (II), (III), (IV), (V), (VI), (VII) and (VIII) as illustrated above, are novel and thus represent a further aspect of the present invention.

In particular, a further aspect of the present invention is intermediate compounds of formulae (VIIIa) and (VIIIb) defined above, with the exception of the following compounds:

(1-Benzyl-1H-indazol-5-yl)-(6-(5-[1,3-dioxolan-2-yl]-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
5-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;
5-(4-(4-Benzyloxy-phenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;
(4-Benzyloxy-phenyl)-(6-(5-[1,3-dioxolan-2-yl]-furan-2-yl)-quinazolin-4-yl)-amine;
5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-[1,3-dioxolan-2-yl]-furan-2-yl)-quinazolin-4-yl)-amine;
5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-carbaldehyde;
5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-1-methyl-pyrrole-2-carbaldehyde;
(1-Benzyl-1H-indazol-5-yl)-(7-(5-[1,3-dioxolan-2-yl]-furan-2-yl)-quinazolin-4-yl)-amine;
5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl)-furan-2-carbaldehyde.

In particular, a yet further aspect of the present invention is intermediate compounds of formula (VIIIc) as defined above;
with the proviso that the following compound is excluded:

(4-Benzyloxy-phenyl)-(6-(5-((2-methanesulphinyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine.

In particular, another further aspect of the present invention is intermediate compounds of formulae (X), (XI), (XII), (XIII), (XIV), (XV) and (XVI) as defined above.

The compounds of formula (I) and salts thereof have anticancer activity as demonstrated hereinafter by their inhibition of the protein tyrosine kinase c-erbB-2, c-erbB-4 and/or EGF-R enzymes and their effect on selected cell lines whose growth is dependent on c-erbB-2 or EGF-r tyrosine kinase activity. Certain compounds of formula (I) are also demonstrated hereinafter to inhibit Ick and/or zap70 protein tyrosine kinase enzymes and are expected to have activity in disease conditions in which T cells are hyperactive.

The present invention thus also provides compounds of formula (I) and pharmaceutically acceptable salts or solvates thereof for use in medical therapy, and particularly in the treatment of disorders mediated by aberrant protein tyrosine kinase activity such as human malignancies and the other disorders mentioned above. The compounds of the present invention are especially useful for the treatment of disorders caused by aberrant c-erbB-2 and/or EGF-r and/or Ick activity such as breast, ovarian, gastric, pancreatic, non-small cell lung, bladder, head and neck cancers, psoriasis and rheumatoid arthritis.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein tyrosine kinase activity, including susceptible malignancies, which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in therapy.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of cancer and malignant tumours.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of psoriasis.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of rheumatoid arthritis

Whilst it is possible for the compounds, salts or solvates of the present invention to be administered as the new chemical, it is preferred to present them in the form of a pharmaceutical formulation.

According to a further feature of the present invention there is provided a pharmaceutical formulation comprising at least one compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain for example 0.5 mg to 1 g, preferably 70 mg to 700 mg, more preferably 5 mg to 100 mg of a compound of the formula (I) depending on the condition being treated, the route of administration and the age, weight and condition of the patient.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The animal requiring treatment with a compound, salt or solvate of the present invention is usually a mammal, such as a human being.

A therapeutically effective amount of a compound, salt or solvate of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian However, an effective amount of a compound of the present invention for the treatment of neoplastic growth, for example colon or breast carcinoma, will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70 kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate of the present invention may be determined as a proportion of the effective amount of the compound per se. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

The compounds of the present invention and their salts and solvates may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in anti-cancer therapy, combination with other chemotherapeutic, hormonal or antibody agents is envisaged. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one other pharmaceutically active agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Certain embodiments of the present invention will now be illustrated by way of example only. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

^{1}H NMR spectra were obtained at 500 MHz on a Bruker AMX500 spectrophotometer, on a Bruker spectrophotometer at 300 MHz, on a Bruker AC250 or Bruker AM250 spectrophotometer at 250 MHz and on a Varian Unity Plus NMR spectrophotometer at 300 or 400 MHz. J values are given in Hz. Mass spectra were obtained on one of the following machines: VG Micromass Platform (electrospray positive or negative), HP5989A Engine (thermospray positive) or Finnigan-MAT LCQ (ion trap) mass spectrometer. Analytical thin layer chromatography (tic) was used to verify the purity of some intermediates which could not be isolated or which were too unstable for full characterisation, and to follow the progess of reactions. Unless otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254). Unless otherwise stated, column chromatography for the purification of some compounds used Merck Silica gel 60 (Art. 1.09385, 230–400 mesh), and the stated solvent system under pressure.

Petrol refers to petroleum ether, either the fraction boiling at 40–60° C., or at 60–80° C.

Ether refers to diethylether.

DMSO refers to dimethylsulphoxide.

THF refers to tetrahydrofuran.

HPLC refers to high pressure liquid chromatography.

NMM refers to N-methylmorpholine

Useful preparative techniques are described in WO96/09294, WO97103069, WO97/13771, WO95/19774, WO96/40142 and WO97/30034; also described in these publications are appropriate intermediate compounds other than those detailed below.

Preparation processes specified in the prior art or in the experimental details below for compounds with a particular basic ring system (1) to (6) above may be suitably adapted for others of these basic ring systems.

General Procedures

(A) Reaction of an Amine with a Bicyclic Species Containing a 4-chloropyrimidine or 4-chloropyridine Ring

The optionally substituted bicyclic species and the specified amine were mixed in an appropriate solvent (typically acetonitrile unless otherwise specified, although ethanol, 2-propanol or DMSO may also be used), and heated to reflux. When the reaction was complete (as judged by tic), the reaction mixture was allowed to cool. The resulting suspension was diluted, e.g. with acetone, and the solid collected by filtration, washing e.g. with excess acetone, and

dried at 60° C. in vacuo, giving the product as the hydrochloride salt. If the free base was required (e.g. for further reaction), this was obtained by treatment with a base e.g. triethylamine; purification by chromatography was then performed if required.

(B) Reaction of a Product from Procedure (A) with a Heteroaryl Tin Reagent

A stirred mixture of the product from Procedure (A), (containing a suitable leaving group such as chloro, bromo, iodo or triflate), a heteroaryl stannane and a suitable palladium catalyst, such as bis(triphenylphosphine)palladium (II) chloride or 1,4-bis(diphenylphosphino)butane palladium (II) chloride (prepared as described in C. E. Housecroft et. al., Inorg. Chem., (1991), 30(1), 125–130), together with other appropriate additives (such as diisopropylethylamine or lithium chloride), were heated at reflux in dry dioxane or another suitable solvent (e.g. DMF) under nitrogen until the reaction was complete. The resulting mixture was generally purified by chromatography on silica.

(C) Removal of a 1,3-dioxolan-2-yl Protecting Group to Liberate an Aldehyde

The compound containing the 1,3-dioxolan-2-yl group was suspended in an appropriate solvent, e.g.THF and treated with hydrochloric acid, either as an aqueous solution (e.g. 2N) or as a solution in dioxane (e.g. 4 molar) and stirred at ambient temperature until the reaction was judged complete (e.g. by tic or LC/MS analysis). Generally the mixture was diluted with water, and the resulting precipitate was collected by filtration, washed with water and dried to give the aldehyde.

(D) Reaction of an Aldehyde with an Amine by Reductive Amination

An aldehyde (such as the product of General Procedure C) and the required primary or secondary amine were stirred together in a suitable solvent (such as dichloromethane) containing glacial acetic acid (4A molecular sieves may also be present) for ca. 1 h. A suitable reducing agent, such as sodium (triacetoxy) borohydride was then added and stirring continued under nitrogen until the reaction was complete (as judged by hplc or tic). The resulting mixture was washed with an aqueous basic solution (e.g. sodium or potassium carbonate) and extracted with a suitable solvent, e.g. dichloromethane. The dried organic phase was evaporated and the residue purified either by column chromatography or by Bond Elut™ cartridge. If desired, the isolated material was then converted into the hydrochloride salt e.g. by treatment with ethereal hydrogen chloride.

(E) Reaction sequence to Prepare Appropriately Substituted Thioamides

E-1 Reaction of an Aminosulfide with Chloroacetonitrile

To a stirred mixture of an aminosulfide and a suitable base such as sodium bicarbonate or sodium carbonate in an appropriate solvent (typically acetonitrile, although DMF or dioxane can be used) was added chloroacetonitrile dropwise. The resulting mixture was heated to reflux until the reaction was complete. The solid was filtered and the filtrate was concentrated to provide the corresponding aminonitrile.

E-2 Trifluoroacetamide Protection of an Aminonitrile

A solution of the aminonitrile (such as the product of general procedure A) and an amine base, such as triethylamine or NMM in a suitable solvent (e.g. dichloromethane), was cooled to 0° C. and trifluoroacetic anhydride was added dropwise. The resulting mixture was stirred at room temperature until the reaction was complete. Water was added and the mixture was extracted with a suitable solvent (e.g. dichloromethane), the organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude product was purified by column chromatography to provide the corresponding trifluoroacetamide.

E-3 Oxidation of a Cyanosulfide

To a stirred solution of a sulfide (such as the product of general procedure E1) in a suitable solvent (typically methanol/water (2:1), although dichloromethane can be used) cooled to 0° C. was added an oxidizing agent (typically oxone, although MCPBA can be used). The resulting mixture was stirred at room temperature until the reaction was complete. The reaction was concentrated to remove any organic solvents, diluted with water, and extracted with an appropriate solvent (e.g. dichloromethane). The organic layer was dried and concentrated to provide the corresponding cyanosulfone.

E-4 Preparation of Thioamides

To a solution of a cyanosulfone (such as the product of general procedure E-3) and an organic base (e.g. triethylamine) in THF was added hydrogen sulfide gas. The resulting mixture was stirred at room temperature until the reaction was complete. The mixture was concentrated and triturated with hexane to provide thioamide.

(F) Reaction Sequence to Prepare an Optionally Substituted Thiazole

F-1 Reaction of a Vinylstannane with a Product from Procedure (A)

A stirred mixture of the optionally substituted bicyclic 4-anilinopyrimidine species, tributyl(1-ethoxyvinyl) stannane (1 to 5 molar equivalents), and a suitable palladium catalyst (0.03 to 0.1 molar equivalents), such as bis (triphenylphosphine) palladium (II) chloride or tetrakis (triphenylphosphine) palladium (O) was heated at reflux in an appropriate solvent (typically acetonitrile, although DMF or dioxane can be used) until the reaction was complete. The resulting mixture was concentrated and generally purified by trituration with diethyl ether to provide the corresponding bicyclic pyrimidine vinyl ether.

F-2 Reaction of a Product from Procedure (F-1) with a Bromination Reagent

A bicyclic pyrimidine vinyl ether (such as the product of general procedure F-1) and 1 equivalent of a bromination reagent, such as N-bromosuccinimide or bromine, were stirred at 0° C. in a suitable solvent (typically 10% aqueous THF or dichloromethane) until the reaction was complete. The resulting mixture was dried over anhydrous magnesium sulfate and concentrated, or in the case of bromine the solid was filtered, to provide the corresponding (α-bromoketone.

F-3 Reaction of a Product from Procedure (F-2) with a Product from Procedure (E-4)

A stirred mixture of an α-bromoketone (such as the product of general procedure F-2) and thioamide from Procedure E-4 in a 1:1 molar ratio was heated to 70–100° C. in an appropriate solvent (typically DMF, although aceto-

nitrile and THF can be used) until the reaction was complete. The resulting mixture was washed with an aqueous basic solution (e.g. sodium carbonate) and extracted with a suitable solvent, e.g. ethyl acetate. The dried organic layer was concentrated and the residue was purified by column chromatography to provide the corresponding trifluoroacetamide aminothiazole.

F-4 Removal of a Trifluoroacetamide Protecting Group to Liberate an Aminothiazole

A mixture of a trifluoroacetamide protected aminothiazole (such as the product of general procedure F-3) in 2M NaOH/methanol (1:1) was stirred at room temperature until the reaction was complete. The mixture was concentrated, poured into water and extracted with an appropriate solvent e.g. 10% MeOH/dichloromethane. The dried organic layer was concentrated, then dissolved in ethyl acetate/MeOH (1:1) and treated with 4M HCl/dioxane. The resulting solid was filtered to provide the corresponding amine hydrochloride salt.

Synthesis of Intermediates

N-5-[N-tert-Butoxycarbonyl)amino]-2-chloropyridine

A stirred solution of 6-chloronicotinic acid (47.3 g), diphenylphosphoryl azide (89.6 g) and triethylamine (46 ml) in t-butanol (240 ml) were heated under reflux under nitrogen for 2.5 hours. The solution was cooled and concentrated in vacuo. The syrupy residue was poured into 3 liters of a rapidly stirred solution of 0.33N aqueous sodium carbonate. The precipitate was stirred for one hour and filtered. The solid was washed with water and dried in vacuo at 70° C. to give the title compound (62 g) as a pale brown solid; m.p. 144–146° C.; δH [$^2H_6$]-DMSO 8.25(1H, d), 7.95 (1H, bd), 7.25 (1H, d), 6.65(1H, bs), 1.51 (9H, s); m/z $(M+1)^+$229.

This material may subsequently be carried forward to the appropriately substituted pyridopyrimidine intermediate according to the procedures as described in WO95/19774, J. Med. Chem., 1996, 39, pp 1823–1835, and J. Chem. Soc., Perkin Trans. 1, 1996, pp 2221–2226. Specific compounds made by such procedures include 6-chloro-pyrido[3,4-d] pyrimidin-4-one and 4,6-dichloro-pyrido[3,4-d]pyrimidine.

2-Amino-4-fluoro-5-iodo-benzoic acid

To a vigorously stirred solution of dichloromethane (700 ml), methanol (320 ml), and 2-amino-4-fluoro-benzoic acid (33.35 grams, 215 mmoles) was added solid sodium hydrogencarbonate (110 grams, 1.31 moles) followed by portion addition of benzyltrimethyl ammonium dichloroiodate (82.5 grams, 237 mmoles). The mixture was allowed to stir for 48 hours. The mixture was filtered to remove the insolubles. The remaining solid residue was washed with 200 ml of dichloromethane. The filtrate was concentrated and redissolved in a one to one mixture of ethyl acetate (1 liter) and a 0.2 N solution of sodium hydroxide (1 liter), added to a 2 liter separatory funnel and extracted. The organic layer was washed with an additional 200 ml of water. The aqueous layers were combined and acidified with 2N hydrochloric acid. The resulting precipitate was collected by suction filtration, washed with water and dried under vacuum at 60° C. to yield 46.5 grams (77%) of the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ: 8.04(d, 1H), 7.1(s, broad, 2H), 6.63(d, 1H). ESI-MS m/z 280 (M−1).

4-Fluoro-5-iodo-isatoic anhydride

Anhydrous dioxane (0.5 liters), 2-amino-4-fluoro-5-iodobenzoic acid (46 grams, 164 mmoles), and trichloromethylchloroformate (97.4 grams, 492 mmoles) were added to a one liter one neck flask equipped with a magnetic stir bar and reflux condenser. The solution was placed under anhydrous nitrogen, stirred and heated to reflux for 16 hours. The reaction mixture was allowed to cool and was poured into one liter of hexanes. The solid was collected by suction filtration, washed with an additional 0.5 liters of hexanes, and dried under vacuum at room temperature to yield 45.5 grams (90%) of the title compound ^1H NMR (400 MHz, DMSO-d_6) δ: 11.86(s, 1H), 8.24(d, 1H), 6.84(d, 1H). ESI-MS m/z 308 (M+1).

4-Chloro-6-bromoquinazoline and 4-Chloro-6-iodoquinazoline were prepared as described in WO 96/09294.

4-Hydroxy-6-iodo-7-fluoroquinazoline

Dimethylformamide (0.5 liters), 4-fluoro-5-iodo-isatoic anhydride (45 grams, 147 mmoles), and formamidine acetate (45.92 grams, 441 mmoles), were combined in a one liter one-neck flask fitted with a magnetic stir bar. The mixture was placed under anhydrous nitrogen and heated at 110° C. for 6 hours. The mixture was allowed to cool, followed by concentrating the reaction mixture to one third its original volume on the rotary evaporator. The resulting mixture was poured onto 3 liters of ice water. The resulting precipitated solid was collected by suction filtration. The solid was washed with an additional one liter of distilled water. The resulting solid was dried under vacuum at 70° C. to yield 38.9 grams (91%) of the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ: 12.43(s, 1H), 8.46(d, 1H), 8.12(s, 1H), 7.49(d, 1H). ESI-MS m/z 291(M+1).

4-Chloro-6-iodo-7-fluoro-quinazoline hydrochloride

Thionyl chloride (0.6 liters), 4-hydroxy-6-iodo-7-fluoroquinazoline (36 grams, 124 mmoles), and dimethylformamide (6 ml) were combined in a one liter one-neck flask fitted with a magnetic stir bar. The mixture was placed under anhydrous nitrogen and heated to a gentle reflux for 24 hours. The mixture was allowed to cool, followed by concentrating the reaction mixture to a thick yellowish residue. To this residue was added dichloromethane (0.1 liter) and toluene (0.1 liter). The mixture was concentrated to dryness. This procedure was repeated two additional times. To the resulting solid was added 0.5 liters of dry dichloromethane and the mixture was stirred for one hour. The mixture was filtered and the remaining solids were washed with minimal dichloromethane. The dichoromethane filtrates were combined, concentrated to a solid, and dried under vacuum at room temperature to yield 28.6 grams (67%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$-d_1) δ: 9.03(s, 1H), 8.76(d, 1H), 7.69(d, 1H). ESI-MS m/z 309(M+1).

2-Bromo-4-(1,3-dioxolan-2-yl) thiazole

2-Bromothiazole-4-carbaldehyde (6.56 g, 34.17 mmol) [A. T. Ung, S. G. Pyne/Tetrahedron: Asymmetry 9 (1998) 1395–1407]and ethylene glycol (5.72 ml, 102.5 mmol) were heated under reflux in toluene (50 ml),with a Dean and Stark trap fitted, for 18 hr. The product was concentrated and purified by column chromatography (15% ethyl acetate/hexane) to give the product as a yellow solid (6.03 g); m/z 236,238.

4-(1,3-Dioxolan-2-yl)-5-(tributylstannyl)thiazole

2-Bromo-4-(1,3-dioxolan-2-yl) thiazole (6.4 g, 27.14 mmol) was stirred at −78° C. in dry THF (38 ml). 1.6M n

butyl lithium in hexane (18.6 ml, 29.78 mmol) was added dropwise under nitrogen. After 30 min at this temperature, tributyl tin chloride (7.35 ml, 27.14 mmol) was added dropwise. The reaction was allowed to warm to 0° and water (20 ml) was added. The product was extracted into ether (3×100 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was triturated with isohexane (3×100 ml) and the mother liquors were decanted, combined and concentrated to give a brown oil (11.88 g); m/z 444–450.

1-N-Benzyl-5-nitro-1H-indazole and 2-N-Benzyl-5-nitro-1H-indazole

A stirred mixture of 5-nitroindazole (50 g), potassium carbonate (46.6 g, 1.1 equiv.) and benzyl bromide (57.6 g, 1.1 equiv) in N,N-dimethylformamide (500 ml) was heated at 75° C. for a period of 4 hours. The reaction was then cooled and water (500 ml) was gradually added to precipitate the product which was filtered off and washed with water (50 ml) and dried in the air at ambient temperature. The weight of pale yellow solid thus obtained was 72.3 g (93%), m.p. 95–97° C.; HPLC (Partisil 5, dichloromethane, 4 ml/min, 250 nm) gave an isomer ratio (1-N-benzyl: 2-N-benzyl) of 63:37 (RT-1N 3.4 min, RT-2N 6.6 min). To a filtered solution of the mixed regioisomers (100 g) in acetone (470 ml) at room temperature was added, gradually with stirring, water (156 ml) and the mixture was stirred for one hour. The resultant yellow crystalline solid was filtered off and dried in the air at ambient temperature to give 36.4 g (34%) of material; m.p. 124–126° C.; HPLC showed an isomer ratio (1-N-benzyl: 2-N-benzyl) of 96:4; δH ($CDCl_3$) 5.58 (2H, s, CH_2), 7.12–7.15(2H) & 7.22–7.29(3H)-(phenyl), 7.33 (1H, dt, J=1 Hz & 9 Hz, H-7), 8.15(1H, dd, J=2 Hz & 9 Hz, H-6), 8.19(1H, d, J=1 Hz, H-3), 8.67 (1H, dd, J=1 Hz & 2 Hz, H-4).

Also note the published method in FR 5600, Jan. 8, 1968.

5-Amino-1-N-benzyl-1H-indazole

1-Benzyl-5-nitroindazole (400 g) was suspended in ethanol (5 liter) and hydrogenated in the presence of 5% platinum on carbon catalyst (20 g) operating at 1 bar pressure and 50–60° C. When hydrogen uptake was complete the reactor contents were heated to 70° C., discharged and filtered while still hot and the filtrate concentrated to ~4 liter which caused some crystallisation. Water (4 liter) was then gradually added with stirring and the mixture was stirred at 5° C. overnight. The resultant crystals were filtered off and air-dried at ambient temperature to give 305 g (86%) of material, m.p. 150–152° C.; HPLC (Supelcosil ABZ+, gradient 0.05% trifluoroacetic acid in water/0.05% trifluoroacetic acid in acetonitrile, 1.5 ml/min, 220 nm) showed <1% of the corresponding 2-N-isomer (RT-1N 6.03 min, RT-2N 5.29 min); δH ($CDCl_3$) 3.3–3.8(2H, broad s, NH_2), 5.47 (2H, s, CH_2), 6.74 (1H, dd, J=2 Hz & 9 Hz, H-6), 6.87 (1H, dd, J=1 Hz & 2 Hz, H-4), 7.06–7.11(3H) & 7.17–7.25 (3H)-(phenyl & H-7), 7.77 (1H, d, J=1 Hz, H-3).

Also note the published method in FR 5600, Jan. 8, 1968.

1-Benzyl-3-methyl-5-nitro-1H-indazole

2-Fluoro-5-nitroacetophenone (H. Sato et al, Bioorganic and Medicinal Chemistry Letters, 5(3), 233–236,1995) (0.24 g) was treated with triethylamine (0.73 ml) and benzyl hydrazine dihydrochloride (0.255 g) in ethanol (20 ml) at reflux under N_2 for 8 days. The mixture was cooled and the solid 1-benzyl-3-methyl-5-nitroindazole (0.16 g) was collected by filtration; m/z $(M+1)^+$268.

1-Benzyl-3-methyl-1H-indazol-5-ylamine

1-Benzyl-3-methyl-5-nitroindazole (0.15 g) in THF (15 ml) was treated with platinum on carbon (0.05 g, 5%) under an atmosphere of hydrogen at room temperature. When hydrogen uptake was complete, the mixture was filtered and concentrated in vacuo to give the title compound; m/z $(M+1)^+$268.

Further Amino-indazole Intermediates

The relevant nitro-substituted 1H-indazole was treated with a base such as potassium carbonate or sodium hydroxide in a suitable solvent, such as acetone or acetonitrile. The appropriate aryl halide or heteroaryl halide was added and the reaction mixture heated or stirred at room temperature overnight. Subsequent concentration in vacuo and chromatography on silica gave the desired 1-substituted nitro-1H-indazoles. Hydrogenation was carried out by analogy with the preparation of 5-amino-1-benzyl-1H-indole described above.

Amines prepared by such methods include:

5-Amino-1-benzyl-1H-indazole; m/z $(M+1)^+$224
5-Amino-1-(2-fluorobenzyl)-1H-indazole; m/z $(M+1)^+$242
5-Amino-1-(3-fluorobenzyl)-1H-indazole; m/z $(M+1)^+$242
5-Amino-1-(4-fluorobenzyl)-1H-indazole; m/z $(M+1)^+$242
5-Amino-1-(2-pyridylmethyl)-1H-indazole; m/z $(M+1)^+$225
5-Amino-1-(3-pyridylmethyl)-1H-indazole; m/z $(M+1)^+$225
5-Amino-1-(4-pyridylmethyl)-1H-indazole; m/z $(M+1)^+$225
5-Amino-1-(2,3-difluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 260
5-Amino-1-(3,5-difluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 260.

1-Benzenesulphonylindol-5-yl-amine was prepared according to the published method (J. Org. Chem., 55,1379–90, (1990)).

4-Benzyloxyaniline is commercially available as the hydrochloride salt; this is treated with aqueous sodium carbonate solution, and the mixture extracted with ethyl acetate; the organic solution is dried ($MgSO_4$) and concentrated to give the free base as a brown solid, used without further purification.

Other substituted anilines were in general prepared by analogous methods to those outlined in WO 96/09294 and/or as follows:

Step 1: Preparation of the Precursor Nitro-compounds

4-Nitrophenol (or an appropriate substituted analogue, such as 3-chloro-4-nitrophenol) was treated with a base such as potassium carbonate or sodium hydroxide in an appropriate solvent, such as acetone or acetonitrile. The appropriate aryl or heteroaryl halide was added and the reaction mixture heated or stirred at room temperature overnight.

Purification A: Most of the acetonitrile was removed in vacuo, and the residue was partitioned between water and dichloromethane. The aqueous layer was extracted with further dichloromethane (×2), and the combined dichloromethane layers were concentrated in vacuo.

Purification B: Removal of insoluble material by filtration, followed by concentration of the reaction mixture in vacuo, and chromatography on silica.

Step 2: Reduction to the Corresponding Aniline

The precursor nitro compound was reduced by catalytic hydrogenation at atmospheric pressure using 5% Pt/carbon, in a suitable solvent (eg ethanol, THF, or mixtures thereof to promote solubility). When reduction was complete, the mixture was filtered through Harborlite™, washing with

excess solvent, and the resulting solution concentrated in vacuo to give the desired aniline. In some cases, the anilines were acidified with HCl (e.g. in a solution in dioxane) to give the corresponding hydrochloride salt.

Anilines prepared by such methods include:

4-(2-Fluorobenzyloxy)aniline; m/z $(M+1)^+$218
4-(3-Fluorobenzyloxy)aniline; m/z $(M+1)^+$218
4-(4-Fluorobenzyloxy)aniline; m/z $(M+1)^+$218
3-Chloro-4-(2-fluorobenzyloxy)aniline; m/z $(M+1)^+$252
3-Chloro-4-(3-fluorobenzyloxy)aniline; m/z $(M+1)^+$252
3-Chloro-4-(4-fluorobenzyloxy)aniline; m/z $(M+1)^+$252
4-Benzyloxy-3-chloroaniline; m/z $(M+1)^+$234
and, in appropriate cases, their hydrochloride salts.

4-Benzenesulphonylaniline was prepared by the published method (Helv. Chim. Acta., 1983, 66(4), p1046.

4-Benzyloxy-3-trifluoromethyl-nitrobenzene

60% NaH dispersion (1.4 g, 33.5 mmol) in mineral oil was washed with hexanes and then suspended in DMF (10 ml). To this NaH suspension in DMF, added benzyl alcohol (2.8 ml, 26.3 mmol) with water bath to keep the temperature below 30 ° C. The reaction mixture was stirred until the evolution of the hydrogen gas ceased. To a solution of 2-fluoro-5-nitrobenzotrifluoride (5.0 g, 23.9 mmol) in DMF (20 ml) was added the benzyl alkoxide solution slowly at 0 ° C. Upon the completion of the addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into 200 ml ice water, stirred until the yellow solid was formed. Filtered and the solid was washed with water and then trituated with pentane. 5.9 g yellow solid was collected (yield: 83%). ESI-MS m/z 298 $(M+H)^+$.

4-Benzyloxy-3-trifluoromethyl-aniline

Raney Ni suspension (about 200 mg Ni) was stirred with methanol. The supernate was decanted. This was repeated twice and then fresh methanol was added. To this suspension of Ni in methanol, was added 2-O-benzyl-5-nitrotrifluoride (375 mg, 1.26 mmol). With the water bath to keep the temperature below 30° C., the hydrazine hydrate (189 mg, 3.79 mmol) was slowly added. Upon the completion of addition, the reaction mixture was stirred at room temperature for 10 minutes and then 45° C. until evolution of nitrogen gas ceased. Filtered through Celite® and the filtrate was concentrated under reduced pressure. 336 mg thick yellow syrup was obtained (yield: 100%). ESI-MS m/z 268 $(M+H)^+$.

4-(Tributylstannyl)thiazole-2-carbaldehyde

4-Bromo-2-(tributylstannyl)thiazole (T. R. Kelly and F. Lang, *Tetrahedron Lett.*, 36, 9293, (1995)) (15.0 g) was dissolved in THF (150 ml) under a nitrogen atmosphere, cooled to −85° C. and treated with t-BuLi (1.7M, in pentane, 43 ml). The mixture was stirred at −85° C. for 30 min, and then N-formylmorpholine (8.4 g) was added by syringe. After further stirring at −85° C. for 10 min the mixture was allowed to warm to room temperature. Water (200 ml) was added and the mixture was extracted with diethyl ether (4×100 ml). The combined ethereal extracts were washed with water, dried ($NaSO_4$), and concentrated in vacuo. Chromatography on silica, eluting with 10%ether/hexane, gave the title compound as a yellow oil; δH $[^2H_6]$DMSO 10.03 (1H, s), 8.29 (1H, s), 1.55 (6H, q), 1.21–1.37 (6H, m), 1.09–1.20 (6H, m), 0.85 (9H, t).

(1-Benzyl-1H-indazol-5-yl)-(6-chloropyrido[3,4-d] pyrimidin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 1-benzyl-1H-indazol-5-ylamine and 4,6-dichloropyrido[3,4-d] pyrimidine; δH $[^2H_6]$-DMSO 9.08 (1H, s), 8.92 (1H, s), 8.82 (1H, s), 8.23 (1H, d), 8.19 (1H, s), 7.80 (1H, d), 7.70 (1H, dd), 7.38–7.22 (5H, m), 5.69 (2H, s); m/z $(M+1)^+$387.

(1-Benzyl-1H-indazol-5-yl)-(6-(5-[1,3-dioxolan-2-yl]-furan-2-yl)-pyrido[3.4-d]-pyrimidin-4-yl)-amine

(1-Benzyl-1H-indazol-5-yl)-(6-chloropyrido[3,4-d] pyrimidin-4-yl)-amine (4.28 g), 2-(tributylstannyl)-5-(1,3-dioxolan-2-yl)-furan (J. Chem Soc., Chem. Commun., (1988), p560) (10 g) and 1,4-bis(diphenylphosphino)butane palladium (II) chloride (1 g) were heated at reflux in dioxane (150 ml) for 24 hr (Procedure B). The solvent was removed in vacuo and the residue chromatographed on silica. Subsequent trituration gave the title compound as a yellow solid; δH $[^2H_6]$-DMSO 10.46 (1H, s), 9.17 (1H, s), 8.74 (1H, s), 8.52 (1H, s), 8.23 (1H, s), 8.18 (1H, s), 7.80–7.68 (2H, m), 7.41–7.22 (5H, m), 7.17 (1H, d), 6.80 (1H, d), 6.06 (1H, s), 5.71 (2H, s), 4.20–3.96 (4H, m).

5-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d] pyrimidin-6-yl)-furan-2-carbaldehyde

(1-Benzyl-1H-indazol-5-yl)-(6-(5-[1,3-dioxolanyl]-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine (3.03 g) and 2N HCl (50 ml) were stirred in THF (50 ml) for 16 hr. The resulting precipitate was filtered and washed with water to give the hydrochloride salt of the product; δH $[^2H_6]$ DMSO 11.70 (1H, s), 9.74 (1H, s) 9.30 (1H, s), 9.27 (1H, s), 8.85 (1H, s), 8.23 (1H, s), 8.18 (1H, s), 7.68–7.87 (3H, m), 7.55 (1H, d), 7.22–7.38 (5H, m), 5.71 (2H, s). Subsequent neutralisation with triethylamine in ethanol/water gave the title compound; δH $[^2H_6]$-DMSO 9.64(1H, s), 9.19 (1H, s), 9.09(1H, s), 8.72(1H, s), 8.12(2H, m), 7.71(2H, m), 7.63 (1H, dd), 7.43(1H, d), 7.20(5H, m), 5.62(2H, s).

(4-Benzyloxyphenyl)-(6-chloro-pyrido[3,4-d] pyrimidin-4-yl)-amine

Prepared according to Procedure A from 4-benzyloxyaniline and 4,6-dichloro-pyrido[3,4-d] yrimidine; δH ($CDCl_3$) 9.11 (1H, s), 8.78 (1H, s), 7.75 (1H, d), 7.56 (2H, dd), 7.40 (5H, m), 7.15 (2H, d), 5.10 (2H, s); m/z $(M+1)^+$409.

5-(4-(4-Benzyloxy-phenylamino)-pyrido[3,4-d] pyrimidin-6-yl)-furan-2-carbaldehyde

(4-Benzyloxyphenyl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine (4.0 g, 11.0 mmol), 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan (J. Chem. Soc., Chem. Commun., (1988), 560) (6.0 g, 14.0 mmol) were reacted together in a procedure analogous to Procedure B above for 20 hrs. The reaction mixture was allowed to cool, 1N HCl (50 ml) added and stirred at room temperature for 15 minutes. The reaction was filtered and the residue washed with dioxane (20 ml) and 2N HCl (20 ml). The combined filtrate and washings were stirred at room temperature for a further hour. The dioxane was removed under vacuum, the reaction diluted with water and the solid which precipitated was collected by filtration, and washed with water, iso-hexane and acetone. This precipitate was converted to the free base by partitioning into a mixture of triethylamine, ethyl acetate and water. The organic phase was washed with water, dried (magnesium sulphate) and the solvent removed under

vacuum. The residue was triturated with iso-hexane/ethyl acetate to give the product (2.41 g, 52%) as a yellow solid; δH [$^2H_6$]-DMSO 10.60 (1H, b, NH), 9.83 (1H, s, CHO), 9.30 (1H, s, 2-H), 9.08 (1H, s, 5-H or 8-H), 8.76 (1H, s, 5-H or 8-H), 7.89 (1H, d, furan-H), 7.82 (2H, d, 2'-H, 6'-H), 7.65–7.42 (6H, m, 5×Ph-H, furan-H), 7.21 (2H, d, 3'-H, 5'-H), 5.26 (2H, s, OCH_2); m/z $(M+1)^+$423.

(4-Benzyloxyphenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine

Reaction of (4-benzyloxyphenyl)-(6-chloro-pyrido[3,4-d] pyrimidin-4-yl)amine (5.44 g, 15.0 mmol), 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan (10.4 g, 24.2 mmol) and bis (triphenylphosphine)palladium (II) chloride (catalytic amount) in dioxane (150 ml) according to Procedure B, followed by purification by silica gel chromatography (eluted with 50–100% EtOAc/i-hexane), allowed the isolation of the dioxolane product (3.45 g, 7.40 mmol, 49%); δH [$^2H_6$]DMSO 10.28 (1H, s), 9.13 (1H, s), 8.69 (1H, s), 8.61 (1H, s), 7.71 (2H, d), 7.31–7.52 (5H, m), 7.14 (1H, d), 7.09 (2H, d), 6.77 (1H, d), 6.03 (1H, s), 5.15 (2H, s), 3.95–4.19 (4H, m). This could then be converted to 5-(4-(4-Benzyloxy-phenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde (identical to that described above) using Procedure C.

(4-Phenoxyphenyl)-(7-iodoquinolin-4-yl)amine

4-Chloro-7-iodoquinoline (10 g, 34 mmol) [Semenov, V. P.; Studenikov, A. N. Synthesis of 7-iodo-4-aminoquinoline derivatives. Khim. Geterotsikl. Soedin. (1980), Issue 7, 972–5] and 4-phenoxyaniline (6.38 g, 34 mmol) in butanol (75 ml) were heated at gentle reflux (120° C.) overnight (18 hrs). On cooling the resultant precipitate was collected by filtration and washed with acetonitrile (2×50 ml). The resultant solid was suspended in chloroform (500 ml) and 2N sodium carbonate solution (300 ml) and heated at 75° C. for 45 mins. On cooling the resultant precipitate was collected by filtration, washed with water (2×50 ml) and dried to yield the product as a pale brown solid. (9.95 g, 66%) δH [$^2H_6$]DMSO 8.35(3H, m), 8.20(1H, s), 8.10(1H, d), 7.85 (1H, s), 7.35(4H, m), 7.15(4H, d), 6.75(1H, d).

(4-Benzyloxyphenyl)-(6-bromoquinazolin-4-yl)-amine hydrochloride

4-Chloro-6-bromoquinazoline (0.25 g, 1.0 mmol) and 4-benzyloxyaniline (0.25 g, 1.3 mmol) were mixed in 2-propanol (6 ml) and heated at reflux for 10 mins (Procedure A). The solution was allowed to cool at room temperature and the 2-propanol removed in vacuo. The resulting solid was triturated with acetone to give the product as a yellow solid (0.39 g, 88%); δH [$^2H_6$]-DMSO 11.60 (1H, b, NH), 9.21 (1H, s, 5-H), 8.86 (1H, s, 2-H), 8.20 (1H, d, 7-H), 7.90 (1H, d, 8-H), 7.65 (2H, d, 2'-H, 6'-H), 7.50–7.25 (5H, m, Ph-H), 7.10 (2H, d, 3'-H, 5'-H), 5.15 (2H, s, CH_2); m/z 405/407 (M+).

(4-Benzyloxyphenyl)-(6-iodoquinazolin-4-yl)-amine hydrochloride

4-Chloro-6-iodoquinazoline (8 g) was treated with 4-benzyloxyaniline (5.5 g) in acetonitrile (500 ml) at reflux under N_2 for 18 hours. Subsequent cooling and filtration gave the title compound (13.13 g); δH [$^2H_6$]-DMSO 11.45 (1H, b, NH), 9.22 (1H, s, 5-H), 8.89 (1H, s, 2-H), 8.36 (1H, d, 7-H), 7.69 (1H, d, 8-H), 7.63 (2H, d, 2'-H, 6'-H), 7.52–7.29 (5H, m, Ph-H), 7.14 (2H, d, 3'-H, 5'-H), 5.18 (2H, s, CH_2); m/z $(M+1)^+$454.

(4-Benzyloxyphenyl)-(6-iodo-7-fluoro-quinazolin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 4-chloro-6-iodo-7-fluoro-quinazoline hydrochloride (4.02 grams, 11.65 mmoles), anhydrous dioxane (70 ml), dichloromethane (20 ml) and 4-benzyloxyaniline hydrochloride (2.83 grams, 12 mmoles). The mixture was stirred and heated to 110° C. (oil bath temperature) for 16 hours. The mixture was cooled to room temperature and filtered to remove the precipitated solids. The solids were washed with cold anhydrous dioxane (100 ml) followed by cold anhydrous diethyl ether. The yellowish solid was collected and dried under vacuum at room temperature to yield 4.68 grams (79%) of the title compound. δH (400 MHz, DMSO-d_6): 11.2(s, 1H), 9.3(d, 1H), 8.79(s, 1H), 7.64(d, 1H), 7.58(d, 2H), 7.44(d, 2H), 7.38(m, 2H), 7.31 (m, 1H), 7.09(d, 2H), 5.14(s, 2H) ESI-MS m/z 472(M+1).

(1-Benzyl-1H-indazol-5-yl)-(6-iodo-7-fluoro-quinazolin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 1-benzyl-1H-indazol-5-ylamine and 4-chloro-6-iodo-7-fluoroquinazoline. δH (400 MHz, DMSO-d_6): 11.55(s, 1H), 9.41(d, 1H), 8.8(s, 1H), 8.18(s, 1H), 8.05(d, 1H), 7.78(d, 1H), 7.69(d, 1H), 7.61(m, 1H), 7.29(m, 2H), 7.23(m, 3H), 5.67(s, 2H). ESI-MS m/z 496(M+1).

(4-Benzenesulphonyl)phenyl-(6-iodo-7-fluoro-quinazolin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 4-(benzenesulphonyl)phenylamine and 4-chloro-6-iodo-7-fluoroquinazoline. ^1H NMR (400 MHz, DMSO-d_6) δ: 10.89 (s, 1H), 9.3(d, 1H), 8.79(s, 1H), 8.07(d, 2H), 8.0(d, 2H), 7.94(d, 2H), 7.67(m, 2H), 7.61(m, 2H). ESI-MS m/z 504 (M−1).

6-Iodo-(4-(3-fluorobenzyloxy)-3-chlorophenyl)-quinazolin-4yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-3-chlorophenyl)amine and 4-chloro-6-iodo-quinazoline. ^1H NMR (DMSO-d6) 9.83 (s, 1H); 8.92 (s, 1H); 8.58 (s, 1H); 8.09 (d, 1H); 8.00 (d, 1H); 7.61 (d, 1H); 7.52 (d, 1H); 7.44 (m, 1H); 7.20–7.33 (m, 3H); 7.15 (m, 1H); 5.21 (s, 2H); MS m/z 506 (M+1).

6-Iodo-(4-(3-fluorobenzyloxy)-3-fluorophenyl)-quinazolin-4yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-3-fluorophenyl)amine and 4-chloro-6-iodo-quinazoline. ^1H NMR (DMSO-d6) 9.83 (s, 1H); 8.92 (s, 1H); 8.57 (s, 1H); 8.08 (d, 1H); 7.85 (d, 1H); 7.53 (d, 1H); 7.50 (d, 1H); 7.43 (m, 1H); 7.30–7.20 (m, 3H); 7.15 (m, 1H); 5.20 (s, 2H); MS m/z 490 (M+1).

6-Iodo-(4-(3-fluorobenzyloxy)-3-methoxyphenyl)-quinazolin-4yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-3-methoxyphenyl)amine and 4-chloro-6-iodo-quinazoline. ^1H NMR 400 MHz (DMSO-d6) 11.29 (bs, 1 H0; 9.14 (s, 1H); 8.87 (s, 1H); 8.32 (d, 1H); 7.62 (d, 1H); 7.42 (m, 1H); 7.34 (d, 1H); 7.29–7.22 (m, 3H); 7.18–7.08 (m, 2H); 5.15 (s, 2H); 3.80 (s, 3H); MS m/z 502 (M+1)

6-Iodo-(4-benzyloxy-3-fluorophenyl)-quinazolin-4-yl)amine

Prepared according to Procedure A from 4-benzyloxy)-3-fluorophenylamine and 4-chloro-6-iodo-quinazoline. ^1H

NMR (DMSO-d6) 9.82 (s, 1H); 8.93 (s, 1H); 8.57 (s, 1H); 8.09 (d, 1H); 7.84 (d, 1H); 7.51 (m, 2H); 7.44 (d, 2H); 7.37 (m, 2H); 7.33 (m, 1H); 7.24 (m, 1H); 5.18 (s, 2H); MS m/z 472 (M+1)

6-Iodo-(4-(3-bromobenzyloxy)-phenyl)-quinazolin-4-yl)amine

Prepared according to Procedure A from (4-(3-bromobenzyloxy)-phenyl)amine and 4-chloro-6-iodo-quinazoline. ^{1}H NMR (DMSO-d6) 9.84 (s, 1H); 8.98 (s, 1H); 8.57 (s, 1H); 8.13 (m, 2H); 7.71 (d, 2H); 7.56 (d, 2H); 7.50 (m, 1H); 7.41 (m, 1H); 7.08 (d, 2H); 5.17 (s, 2H).

6-Iodo-(4-(3-fluorobenzyloxy)-phenyl)-quinazolin-4-yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-phenyl)amine and 4-chloro-6-iodo-quinazoline. ^{1}H NMR (DMSO-d6) 9.77 (s, 1H); 8.92 (s, 1H); 8.50 (s, 1H); 8.06 (d, 1H); 7.66 (d, 2H); 7.50 (d, 1H); 7.42 (m, 1H); 7.30–7.25 (m, 2H); 7.14 (m, 1H); 7.03 (d, 2H); 5.13 (s, 2H); MS m/z 472 (M+1)

6-Iodo-(4-(3-trifluoromethylbenzyloxy)-phenyl)-quinazolin-4-yl)amine

Prepared according to Procedure A from (4-(3-trifluoromethylbenzyloxy)-phenyl)amine and 4-chloro-6-iodo-quinazoline. ^{1}H NMR (DMSO-d6) 9.2 (bs, 1H); 8.91 (s, 1H); 8.37 (d, 1H); 7.89–7.72 (m, 8H); 7.19 (d, 2H); 5.30 (s, 2H).

6-Iodo-(4-benzyloxy-3-trifluoromethyl-phenyl)-quinazolin-4-yl)amine

The mixture of 4-chloro-6-iodo-quinazoline (366 mg, 1.26 mmol) and 4-O-benzyl-3-trifluoroaniline (405 mg, 1.26 mmol) in isopropanol (12 ml) was heated to reflux for 3.5 hours. Filtered, washed with isopropanol and dried. 535 mg yellow solid was afforded. (yield: 76%). ESI-MS m/z 522 $(M+H)^+$.

(4-Benzyloxyphenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-fluoro-quinazolin-4-yl)-amine

Synthesized according to Procedure B from a solution of (4-benzyloxyphenyl)-(6-iodo-7-fluoro-quinazolin-4-yl)-amine hydrochloride (508 mg, 1 mmole), 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan (645 mg, 1.5 mmole), diisopropylethyl amine (650 mg, 5 mmole), and dichlorobis (triphenylphosphine) palladium (140 mg, 0.2 mmole) in 6 ml of DMF under nitrogen was stirred at 100° C. (oil bath temperature) for 4 hours. The cooled reaction mixture was extracted with water (100 ml) and ethyl acetate (100 ml). The organic phase was washed with brine (100 ml). The aqueous layers were combined and washed with additional ethyl acetate (100 ml). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated to a residue. The residue was chromatographed on silica gel with a methanol-chloroform mixture. Fractions were collected, combined, and concentrated. The resultant solid was suspended in dichloromethane (10 ml) and diethyl ether was added facilitate precipitation. The solid was filtered and dried under vacuum at room temperature to yield a yellowish solid 287 mg (59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.1(s, 1H), 8.85(d, 1H), 8.45(s, 1H), 7.6(m, 3H), 7.44(d, 2H), 7.38(m, 2H), 7.31 (m, 1H), 7.03(m, 2H), 6.94(m, 1H), 6.74(d, 1H), 6.01(s, 1H), 5.1(s, 2H), 4.10(m, 2H), 3.96(m, 2H). ESI-MS m/z 482(M−1).

(1-Benzyl-1H-indazol-5-yl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-fluoro-quinazolin-4-yl)-amine

Prepared according to Procedure B from (1-benzyl-1H-indazol-5-yl)-(6-iodo-7-fluoro-quinazolin-4-yl)-amine hydrochloride and 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl) furan. δ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27(s, 1H), 8.89(d, 1H), 8.46(s, 1H), 8.1(d, 2H), 7.69(d, 1H), 7.61(m, 2H), 7.26(m, 5H), 6.96(m, 1H), 6.74(d, 1H), 6.01 (s, 1H), 5.65(s, 2H), 4.09(m, 2H), 3.96(m, 2H). ESI-MS m/z 506 (M−1).

(4-Benzenesulphonyl)phenyl-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-fluoro-quinazolin-4-yl)-amine

Prepared according to Procedure B from (4-benzenesulphonyl)phenyl-(6-iodo-7-fluoro-quinazolin-4-yl)-amine hydrochloride and 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan. δ^{1}H NMR (400 MHz, DMSO-d_6) 10.49(s, 1H), 8.88(d, 1H), 8.63(s, 1H), 8.1(d, 2H), 7.95(m, 4H), 7.65(m, 4H), 6.97(m, 1H), 6.75(d, 1H), 6.01(s, 1H), 4.09(m, 2H), 3.97(m, 2H). ESI-MS m/z 516(M−1).

(4-Benzyloxyphenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-quinazolin-4-yl)-amine

Prepared according to Procedure B from (4-benzyloxyphenyl)-(6-bromoquinazolin-4-yl)-amine (1.5 g, 3.7 mmol) and 5-(1,3-dioxolan-2-yl)-2(tributylstannyl)-furan (1.9 g, 4.42 mmol) dissolved in dioxan (30 ml) and heated at reflux under nitrogen for 6 hr. The solvent was removed from the cooled reaction under vacuum, and the residual oil was triturated with iso-hexane/ethyl acetate to give the product (1.07 g, 62%) as a pale yellow solid; δH [$^2H_6$]-DMSO 9.96 (1H, b, NH), 8.80 (1H, s, 5-H), 8.51 (1H, s, 2-H), 8.18 (1H, d, 7-H), 7.80 (1H, d, 8-H), 7.70 (2H, d, 2'-H, 6'-H), 7.58–7.30 (5H, m, 5×Ph-H), 7.10 (3H, m, 3'-H, 5'-H, furan 3-H), 6.78 (1H, d, furan 4-H), 6.12 (1H, s, CHO_2), 5.18 (2H, s, Ph$C\underline{H}_2$), 4.22–3.94 (4H, m, 2×CH_2); m/z 466 $(M+1)^+$.

(4-Benzyloxy-3-trifluoromethylphenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-quinazolin-4-yl)-amine

Prepared according to Procedure B using 6-Iodo-(4-benzyloxy-3-trifluoromethyl-phenyl)-quinazolin-4-yl) amine (480 mg, 0.92 mmol), and 5-tributyltin-(1,3-dioxolan-2-yl)-furan (731 mg, 1.38 mmol) in dioxane (10 ml). The resulting product was a yellow solid (0.47 g, 95.8% yield). ESI-MS m/z 534 $(M+H)^+$.

5-(4-(4-Benzyloxy-3-trifluoromethylphenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde

Prepared according to Procedure C using (4-Benzyloxy-3-trifluoromethylphenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-quinazolin-4-yl)-amine (470 mg, 0.88 mmol) solution in THF (5 ml) followed by the addition of 2N HCl (20 ml) at room temperature. The resulting mixture was stirred for 30 minutes. Water was added (15 ml) then filtered. The yellow solid was washed with water and small amount of ether and dried in vacuo (0.39 g, 84% yield). ESI-MS m/z 490 $(M+H)^+$.

(4-Benzyloxyphenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-methoxy-quinazolin-4-yl)-amine

Prepared according to Procedure B from a solution of (4-benzyloxyphenyl)-7-methoxy-6-trifluoromethanesulphonyl-quinazolin-4-yl)-amine (0.30 g, 0.59 mmol), 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan

(0.37 g, 0.86 mmol), lithium chloride (78 mg, 1.8 mmol), and dichloro-bis(triphenylphosphine)palladium (90 mg, 0.13 mmol) in 2 ml of DMF under nitrogen was stirred at 85–90° C. for 50 minutes. The cooled reaction mixture was partitioned between 30 ml of water and 40 ml of ethyl acetate. The organic solution was washed with 30 ml of brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel with hexanes/ethyl acetate (1:1 to 0:1). The resulting solution was concentrated to near dryness and the resulting solid suspended in ether and filtered to give 0.232 g of product as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.90(s, 1H), 8.71(s, 1H), 8.40(s, 1H), 7.60(d, 2H), 7.44(d, 2H), 7.37(t, 2H), 7.30(t, 1H), 7.24(s, 1H), 7.00(m, 3H), 6.67(d, 1H), 5.99(s, 1H), 5.09(s, 2H), 4.10(m, 2H), 4.02(s, 3H), 3.95(m, 2H). ESI-MS m/z 496(M+1).

(4-Benzyloxyphenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-fluoro-quinazolin-4-yl)-amine

Prepared according to Procedure B from a solution of (4-benzyloxyphenyl)-(6-iodo-7-fluoro-quinazolin-4-yl)-amine hydrochloride (508 mg, 1 mmole), 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan (645 mg, 1.5 mmole), diisopropylethyl amine (650 mg, 5 mmole), and dichlorobis (triphenylphosphine) palladium (140 mg, 0.2 mmole) in 6 ml of DMF under nitrogen was stirred at 100° C. (oil bath temperature) for 4 hours. The cooled reaction mixture was extracted with water (100 ml) and ethyl acetate (100 ml). The organic phase was washed with brine (100 ml). The aqueous layers were combined and washed with additional ethyl acetate (100 ml). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated to a residue. The residue was chromatographed on silica gel with a methanol-chloroform mixture. Fractions were collected, combined, and concentrated. The resultant solid was suspended in dichloromethane (10 ml) and diethyl ether was added to facilitate precipitation. The solid was filtered and dried under vacuum at room temperature to yield a yellow solid 287 mg (59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.1 (s, 1H), 8.85 (d, 1H), 8.45 (s, 1H), 7.6 (m, 3H), 7.44 (d, 2H), 7.38 (m, 2H), 7.31 (m, 1H), 7.03 (m, 2H), 6.94 (m, 1H), 6.74 (d, 1H), 6.01 (s, 1H), 5.1 (s, 2H), 4.10 (m, 2H), 3.96 (m, 2H). ESI-MS m/z 482(M−1).

(4-Benzyloxyphenyl)-(6-iodo-7-fluoro-quinazolin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 4-chloro-6-iodo-7-fluoro-quinazoline hydrochloride (4.02 grams, 11.65 mmoles), anhydrous dioxane (70 ml), dichloromethane (20 ml), and 4-benzyloxyaniline hydrochloride (2.83 grams, 12 mmoles). The mixture was stirred and heated to 110° C. (oil bath temperature) for 16 hours, cooled to room temperature and filtered to remove the precipitated solids. The solids were washed with cold anhydrous dioxane (100 ml) followed by cold anhydrous diethyl ether. The yellowish solid was collected and dried under vacuum at room temperature to yield 4.68 grams (79%) of the title compound. δH NMR (400 MHz, DMSO-d_6): 11.2(s, 1H), 9.3(d, 1H), 8.79(s, 1H), 7.64(d, 1H), 7.58(d, 2H), 7.44(d, 2H), 7.38(m, 2H), 7.31 (m, 1H), 7.09(d, 2H), 5.14(s, 2H) ESI-MS m/z 472(M+1).

(1-Benzyl-1H-indazol-5-yl)-(6-iodo-7-fluoro-quinazolin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 1-benzyl-1H-indazol-5-ylamine and 4-chloro-6-iodo-7-fluoroquinazoline. δH NMR (400 MHz, DMSO-d_6): 11.55(s, 1H), 9.41(d, 1H), 8.8(s, 1H), 8.18(s, 1H), 8.05(d, 1H), 7.78(d, 1H), 7.69(d, 1H), 7.61(m, 1H), 7.29(m, 2H), 7.23(m, 3H), 5.67(s, 2H). ESI-MS m/z 496(M+1).

(4-Benzenesulphonyl)phenyl-(6-iodo-7-fluoro-quinazolin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 4-benzenesulphonyl)phenylamine and 4-chloro-6-iodo-7-fluoroquinazoline. 8HNMR (400 MHz, DMSO-d_6) δ: 10.89 (s, 1H), 9.3(d, 1H), 8.79(s, 1H), 8.07(d, 2H), 8.0(d, 2H), 7.94(d, 2H), 7.67(m, 2H), 7.61(m, 2H). ESI-MS m/z 504 (M−1).

6-Iodo-(4-(3-fluorobenzyloxy)-3-chlorophenyl)-quinazolin-4yl)amine

Prepared according to Procedure A from 4-(3-fluorobenzyloxy)-3-chlorophenyl)-amine and 4-chloro-6-iodoquinazoline. ^{1}H NMR (DMSO-d6) 9.83 (s, 1H); 8.92 (s, 1H); 8.58 (s, 1H); 8.09 (d, 1H); 8.00 (d, 1H); 7.61 (d, 1H); 7.52 (d, 1H); 7.44 (m, 1H); 7.20–7.33 (m, 3H); 7.15 (m, 1H); 5.21 (s, 2H); MS m/z 506 (M+1)

6-Iodo-(4-(3-fluorobenzyloxy)-3-fluorophenyl)-quinazolin-4yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-3-fluorophenyl)-amine and 4-chloro-6-iodoquinazoline. ^{1}H NMR (DMSO-d6) 9.83 (s, 1H); 8.92 (s, 1H); 8.57 (s, 1H); 8.08 (d, 1H); 7.85 (d, 1H); 7.53 (d, 1H); 7.50 (d, 1H); 7.43 (m, 1H); 7.30–7.20 (m, 3H); 7.15 (m, 1H); 5.20 (s, 2H); MS m/z 490 (M+1)

6-Iodo-(4-(3-fluorobenzyloxy)-3-methoxyphenyl)-quinazolin-4yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-3-fluorophenyl)-amine and 4-chloro-6-iodoquinazoline. ^{1}H NMR 400 MHz (DMSO-d6) 11.29 (bs, 1H0; 9.14 (s, 1H); 8.87 (s, 1H); 8.32 (d, 1H); 7.62 (d, 1H); 7.42 (m, 1H); 7.34 (d, 1H); 7.29–7.22 (m, 3H); 7.18–7.08 (m, 2H); 5.15 (s, 2H); 3.80 (s, 3H); MS m/z 502 (M+1)

6-Iodo-(4-benzyloxy-3-fluorophenyl)-quinazolin-4-yl)amine

Prepared according to Procedure A from (4-benzyloxy-3-fluorophenyl)-amine and 4-chloro-6-iodoquinazoline. ^{1}H NMR (DMSO-d6) 9.82 (s, 1H); 8.93 (s, 1H); 8.57 (s, 1H); 8.09 (d, 1H); 7.84 (d, 1H); 7.51 (m, 2H); 7.44 (d, 2H); 7.37 (m, 2H); 7.33 (m, 1H); 7.24 (m, 1H); 5.18 (s, 2H), MS m/z 472 (M+1)

6-Iodo-(4-(3-bromobenzyloxy)-phenyl)-quinazolin-4-yl)amine

Prepared according to Procedure A from (4-(3-bromobenzyloxy)-phenyl)-amine and 4-chloro-6-iodoquinazoline. ^{1}H NMR (DMSO-d6) 9.84 (s, 1H); 8.98 (s, 1H); 8.57 (s, 1H); 8.13 (m, 2H); 7.71 (d, 2H); 7.56 (d, 2H); 7.50 (m, 1H); 7.41 (m, 1H); 7.08 (d, 2H); 5.17 (s, 2H).

6-Iodo-(4-(3-fluorobenzyloxy)-phenyl)-quinazolin-4-yl)amine

Prepared according to Procedure A from (4-(3-fluorobenzyloxy)-phenyl)-amine and 4-chloro-6-iodoquinazoline. ^{1}H NMR (DMSO-d6) 9.77 (s, 1H); 8.92 (s, 1H); 8.50 (s, 1H); 8.06 (d, 1H); 7.66 (d, 2H); 7.50 (d, 1H); 7.42 (m, 1H); 7.30–7.25 (m, 2H); 7.14 (m, 1H); 7.03 (d, 2H); 5.13 (s, 2H), MS m/z 472 (M+1)

6-Iodo-(4-(3-trifluoromethylbenzyloxy)-phenyl)-quinazolin-4-yl)amine

Prepared according to Procedure A from (4-(3-trifluoromethylbenzyloxy)-phenyl)-amine and 4-chloro-6-iodoquinazoline. ^{1}H NMR (DMSO-d6) 9.2 (bs, 1H); 8.91 (s, 1H); 8.37 (d, 1H); 7.89–7.72 (m, 8H); 7.19 (d, 2H); 5.30 (s, 2H).

4-(4-(4-Phenoxyphenylamino)-quinolin-7-yl) thiazole-2-carbaldehyde

Prepared according to Procedure B from (4-phenoxyphenyl)-(7-iodoquinolin-4-yl)amine (2 g, 4.56 mmol), 4-(tributylstannyl)thiazole-2-carbaldehyde (1.84 g, 4.56 mmol) and dichlorobis(triphenylphosphine)palladium (II) (0.74 g, 20 mol %) heated at reflux overnight (18 hrs) in dioxane (50 ml). The cooled solution was filtered through a plug of Celite®, concentrated and triturated with iso-hexane (3×20 ml). The resultant solid was purified via flash column chromatography on silica gel, eluting with 5% methanol in chloroform. The purified product was isolated as a yellow solid (0.85 g, 44%). δH [$^2H_6$]DMSO 10.10(1H, s), 9.30(1, bs), 8.90(1H, s), 8.50(2H, s&d), 8.45(1H, d), 8.20(1H, d), 7.40(5H, bm), 7.10(4H, 2d), 6.80(1H, d).

5-(4-(4-Phenoxyphenylamino)-quinolin-7-yl) thiazole-4-carbaldehyde

Prepared according to Procedure B from (4-phenoxyphenyl)-(7-iodoquinolin-4-yl)amine (0.876 g, 2 mmol), 4-(1,3-dioxolan-2-yl)-5-tributylstannylthiazole (2.1 mmol), bis (triphenylphosphine) palladium (II) chloride (0.105 g, 0.15 mmol, 7.5 mol %) and silver oxide (0.463 g, 2 mmol) heated under reflux under nitrogen for 18 hr. The reaction mixture was then filtered through Harborlite® and the filtrate was concentrated. The product was purified on Bond Elut™ cartridge, eluting sequentially with dichloromethane, chloroform, diethyl ether and ethyl acetate. The ketal (0.385 g, 0.824 mmol) was stirred at room temperature in a mixture of THF (10 ml) and 1 N HCl (10 ml) for 2 hr. The suspension was basified with 2N NaOH (5 ml) and the THF was removed. The aqueous suspension was filtered and washed with water to give the product as a yellow solid (0.346 g);m/z 424.

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde

Prepared according to Procedure C from 4-(4-benzyloxy-phenylamino)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-quinazolin-4-yl)-amine (1.0 g, 2.1 mmol). The precipitate which formed was collected by filtration and washed with acetone, then partitioned between ethyl acetate, triethylamine and water. The organic phase was washed with water, dried (magnesium sulphate) and the solvent was removed under vacuum. Trituration with iso-hexane/ethyl acetate gave the product as an orange solid (610 mg, 69%); δH [$^2H_6$]-DMSO 10.05 (1H, b, NH), 9.62 (1H, s, CHO), 8.95 (1H, s, 5-H), 8.48 (1H, s, 2-H), 8.24 (1H, d, 7-H), 7.80 (1H, d, 8-H), 7.70 (1H, d, furan 4-H), 7.59 (2H, d, 2'-H, 6'-H), 7.48–7.25 (6H, m, 5×Ph-H, furan 3-H), 7.02 (2H, m, 3'-H, 5'-H), 5.09 (2H, s, CH_2); m/z 422 $(M+1)^+$.

5-(4-(4-Benzyloxy-phenylamino)-7-methoxy-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride

Prepared according to Procedure C from (4-benzyloxyphenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-methoxy-pyrido[3,4-d]pyrimidin-4-yl)-amine(0.301 g, 0.60 mmol). After stirring 45 minutes, the resulting suspension was filtered and washed with ether to give 0.26 g of product as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.67(br s, 1H), 9.68(s, 1H), 9.14(s, 1H), 8.78(s, 1H), 7.73(d, 1H), 7.52(d, 2H), 7.44(m, 3H), 7.39(m, 3H), 7.32(m, 1H), 7.11(d, 2H), 5.14(s, 2H), 4.12(s, 3H). ESI-MS m/z 452(M+1).

6-(5-(1.3-Dioxolan-2-yl)-furan-2-yl)-7-methoxy-quinazolin-4-yl-(4-benzenesulphonyl)phenyl-amine

Prepared according to Procedure B from 4-(4-benzenesulphonyl)phenyl-7-methoxy-quinazolin-4-yl-amine and 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan. δ^{1}H NMR (400 MHz, DMSO-d_6) 10.36(s, 1H), 8.74(s, 1H), 8.58(s, 1H), 8.10(d, 2H), 7.93(m, 4H), 7.62(m, 3H), 7.32(s, 1H), 7.04(d, 1H), 6.68(d, 1H), 5.99(s, 1H), 4.09(m, 2H), 4.04(s, 3H), 3.95(m, 2H). ESI-MS m/z 530(M+1).

5-(4-(4-Phenoxyphenylamino)-quinolin-7-yl)furan-2-carbaldehyde

(4-Phenoxyphenyl)-(7-(5-(1,3-dioxolan-2-yl)furan-2-yl)-quinolin-4-yl)amine (1.4 g) was treated with 1M aqueous hydrochloric acid-tetrahydrofuran (60 ml, 1:1) in accordance with procedure C. Addition of 1 M aqueous sodium hydroxide solution to pH 10 followed by extraction with ethyl acetate, drying (magnesium sulfate) and concentration to dryness afforded a yellow solid (1.2 g); δH [$^2H_6$]DMSO 9.70 (1H, s), 9.10 (1H, s), 8.51 (2H, m), 8.35 (1H, s), 8.02 (1H, d), 7.73 (1H, d), 7.57 (1H, d), 7.42 (4H, m), 7.22–7.04 (5H, m), 6.88 (1H, d); m/z 407 $(M+1)^+$.

5-(7-Methoxy-4-(4-benzenesulphonyl)phenylamino-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride

Prepared according to Procedure C from 6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-methoxy-quinazolin-4-yl-(4-benzenesulphonyl)phenyl-amine. δ^{1}H NMR (400 MHz, DMSO-d_6) 11.54(br s, 1H), 9.68(s, 1H), 9.13(s, 1H), 8.83(s, 1H), 7.95–8.06(m, 6H), 7.72(d, 1H), 7.68(m, 1H), 7.62(m, 2H), 7.46(s, 1H), 7.39(d, 1H), 4.12(s, 3H). ESI-MS m/z 486(M+1).

5-(4-(4-Benzyloxy-phenylamino)-7-fluoro-quinazolin-6-yl)-furan-2-carboxaldehyde hydrochloride

Prepared according to Procedure C from a stirred solution of (4-7-benzyloxyphenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-fluoro-quinazolin-4-yl)-amine (0.51 grams, 1.1 mmol) in 20 ml of THF was added 5 ml of 1 N HCl. After stirring for 90 minutes, the resultant suspension was filtered and washed with diethyl ether (200 ml) to yield, after drying under vacuum, a yellow solid (0.32 grams, 61% yield). δ^{1}H NMR (400 MHz, DMSO-d_6) 11.52(s, 1H), 9.70(s, 1H), 9.25(d, 1H), 8.76(s, 1H), 7.76(m, 2H), 7.55(d, 2H), 7.45(d, 2H), 7.33(m, 4H), 7.11(d, 2H), 5.14(s, 2H). ESI-MS m/z 440(M+1).

5-(4-(1-Benzyl-1H-indazol-5-ylamino)-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride

Prepared according to Procedure C from (1-benzyl-1H-indazol-5-ylamino)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-fluoro-quinazolin-4-yl)-amine. δ^{1}H NMR (400 MHz, DMSO-d_6) 11.68(s, 1H),9.71 (s, 1H), 9.28(d, 1H), 8.74(s,

1H), 8.12(s, 1H), 8.02(s, 1H), 7.78(m, 3H), 7.58(m, 2H), 7.3(m, 5H), 5.65(s, 2H). ESI-MS m/z 462(M−1).

5-(4-(4-Benzenesulphonylphenylamino)-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride

Prepared according to Procedure C from 6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-fluoro-quinazolin-4-yl-(4-benzenesulphonyl)phenyl-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.96(s, 1H), 9.7(s, 1H), 9.16(d, 1H), 8.72(s, 1H), 8.07(d, 2H), 7.96(m, 4H), 7.75(m, 2H), 7.64(m, 3H), 7.29(m, 1H. ESI-MS m/z 472(M−1).

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride

Prepared according to Procedure C from 4-(4-benzyloxyphenylamino)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-quinazolin-4-yl)-amine (6.70 g, 14.4 mmol). The resulting precipitate was collected by filtration and washed with water to give the hydrochloride salt as a yellow solid (6.50 g, 14.1 mmol, 98%); δH [$^2H_6$]DMSO 12.15 (1H, s), 9.69 (1H, s) 9.58 (1H, s), 8.88 (1H, s), 8.50 (1H, dd), 8.02 (1H, d), 7.77 (1H, d), 7.62–7.74 (3H, m), 7.31–7.52 (5H, m), 7.15 (2H, d), 5.17 (2H, s).

(4-Phenoxyphenyl)-(7-(5-(1,3-dioxolan-2-yl)furan-2-yl)-quinolin-4-yl)amine

(4-Phenoxyphenyl)-(7-iodo-quinolin-4-yl)amine (2 g) was treated with 2-to (tributylstannyl)-5-(1,3-dioxolan-2-yl)-furan (2.16 g) and tetrakis (triphenylphosphine) palladium (0) (0.26 g) in dimethylacetamide (20 ml) in accordance with Procedure B. Purification via column chromatography, eluting with ethyl acetate, followed by trituration with diethylether afforded a yellow solid (1.4 g); δH [$^2H_6$]DMSO 9.10 (1H, s), 8.45 (2H, m), 8.13 (1H, s), 7.96 (1H, d), 7.41 (4H, m), 7.22 (1H, d), 7.20–7.03 (5H, m), 6.83 (1H, d), 6.75 (1H, d), 6.02 (1H, s), 4.13 (2H, m), 4.01 (2H, m); m/z 451 $(M+1)^+$.

(1-Benzyl-1H-indazol-5-yl)-(6-bromoquinazolin-4-yl)-amine

Prepared according to Procedure A from 6-bromo-4-chloroquinazoline (5.0 g) and 5-amino-1-benzyl-1H-indazole (5.0 g) in acetonitrile (100 ml) at 100° C. The resulting precipitate was treated with triethylamine in ethyl acetate and water to give the title compound as a yellow solid, (7.37 g); δH [$^2H_6$]-DMSO 9.93(1H, s), 8.82 (1H, d), 8.52(1H, s), 8.19(1H, s), 8.09(1H, s), 7.92(1H, dd), 7.65(3H, m), 7.25(5H, m), 5.62(2H, s).

(1-Benzyl-1H-indazol-5-yl)-(6-iodoquinazolin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 4-chloro-6-iodoquinazoline (5.8 g) was treated with 5-amino-1-benzyl-1H-indazole (3.90 g) in acetonitrile (500 ml) at reflux under N_2 for 18 hours. Subsequent cooling and filtration gave the title compound (8.26 g); m/z $(M+1)^+$478.

(1-Benzyl-1H-indazol-5-yl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-quinazolin-4-yl)-amine

Prepared according to Procedure B from (1-benzyl-1H-indazol-5-yl)-(6-bromoquinazolin-4-yl)-amine (4.3 g), 2-(tributylstannyl)-5-(1,3-dioxolan-2-yl)-furan (J. Chem. Soc., Chem Commun., (1988), 560) (10 g) and 1,4-bis (diphenylphosphino) palladium (II) chloride (1 g) in dioxane. The solvent was removed in vacuo and the residue chromatographed on silica. Subsequent trituration gave the title compound δH [$^2H_6$]-DMSO 10.13 (1H, s), 8.85 (1H, s), 8.54 (1H, s), 8.20 (3H, m), 7.80 (3H, m), 7.30 (5H, m), 7.13 (1H, d), 6.79 (1H, d), 6.04 (1H, s), 5.71 (2H, s), 4.15 (4H, m).

(1-Benzyl-1H-indazol-5-yl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-methoxy-quinazolin-4-yl)-amine

Prepared according to Procedure B from (1-benzyl-1H-indazol-5-yl)-7-methoxy-6-trifluoromethanesulphonyl-quinazolin-4-yl)-amine and 2-(tributylstannyl)-5-(1,3-dioxolan-2-yl)-furan. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.07(s, 1H), 8.75(s, 1H), 8.42(s, 1H), 8.09(s, 2H), 7.64(m, 2H), 7.2–7.3(m, 6H), 7.01(d, 1H), 6.68(d, 1H), 5.99(s, 1H), 5.64(s, 2H), 4.09(m, 2H), 4.03(s, 3H), 3.94(m, 2H). ESI-MS m/z 520(M+1).

5-(4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride

Prepared according to Procedure C from (1-benzyl-1H-indazol-5-yl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-quinazolin-4-yl)-amine (2.0 g). The resulting precipitate was filtered, washed with water and dried at 60° C. in vacuo to give the product as a yellow solid (1.80 g, 3.73 g, 91%); δH [$^2H_6$]-DMSO 12.30 (1H, s), 9.79 (1H, s), 9.62 (1H, s), 8.85 (1H, s), 8.62 (1H, m), 8.31 (1H, s), 8.19 (1H, m), 8.10 (1H, d), 7.90 (2H, m), 7.78 (2H, m), 7.40 (5H, m), 5.80 (2H, s).

5-(4-(1-Benzyl-1H-indazol-5-yl)-7-methoxy-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride

Prepared according to Procedure C from (1-benzyl-1H-indazol-5-yl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-7-methoxy-quinazolin-4-yl)-amine. δH NMR (400 MHz, DMSO-d_6): 11.94(br s, 1H), 9.68(s, 1H), 9.20(s, 1H), 8.79(s, 1H), 8.19(s, 1H), 7.97(d, 1H), 7.81(d, 1H), 7.74(d, 1H), 7.57(m, 1H), 7.44(s, 1H), 7.41(d, 1H), 7.30(m, 2H), 7.24(m, 3H), 5.68(s, 2H), 4.13(s, 3H). ESI-MS m/z 476(M+1).

7-Iodoquinazolin-4-one

7-Amino-quinazolin-4-one (R. Dempsy and E. Skito, Biochemistry, 30, 1991, 8480) (1.61 g) was suspended in 6N HCl (20 ml) and cooled in an ice bath. A solution of sodium nitrite (0.75 g) in water (10 ml) was added dropwise over 15 minutes. After a further 10 minutes, a solution of potassium iodide (1.66 g) in water (5 ml) was added dropwise. The mixture was warmed to 20° C. and after 3 hours partitioned between ethyl acetate and sodium thiosulphate. The organic phase was dried and concentrated in vacuo to give the title compound (0.485 g); m/z (M+1+) 271.

4-Chloro-7-iodoquinazoline

7-Iodoquinazolin-4-one (0.46 g) was treated with phosphorous oxychloride (5 ml) at reflux under nitrogen for 2 hours. The mixture was cooled, evaporated and it partitioned between saturated aqueous sodium carbonate and ethyl acetate. The organic phase was dried and concentrated in vacuo to give the title compound (0.43 g); m/z (M+1+) 291.

(1-Benzyl-1H-indazol-5-yl)-(7-iodoquinazolin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 4-Chloro-7-iodoquinazoline (0.42 g) and 1-benzyl-1H-indazol-5-ylamine (0.323 g) in acetonitrile (20 ml) at reflux under

nitrogen for 18 hours. The mixture was cooled and filtered to give the title compound (0.57 g); m/z (M+1+) 478.

(1-Benzyl-1H-indazol-5-yl)-[7-(5-(1,3-dioxolan-2-yl)-furan-2-yl)quinazolin-4-yl]amine hydrochloride

Prepared according to Procedure B from (1-benzyl-1H-indazol-5-yl)-(7-iodoquinazolin-4-yl)-amine hydrochloride and 5-(1,3-dioxolan-2-yl)-2-(tri-n-butylstannyl)furan; tlc Rf, 0.25 (100% EtOAc on silica); m/z (M+1+) 490.

5-[4-(1-Benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl]-furan-2-carbaldehyde

Prepared according to Procedure C from (1-benzyl-1H-indazol-5-yl)-[7-(5-(1,3-dioxolan-2-yl)furan-2-yl) quinazolin-4-yl]-amine hydrochloride (0.27 g) stirred in THF:2N HCl (2:1, 15 ml) at 20° C. for 1 hour. Filtration gave 5-[4-(1-benzyl-1H-indazol-5-ylamino)-quinazolin-7-yl]-furan-2-carbaldehyde, which was not further characterised.

(4-Benzyloxy-phenyl)-(6-((5-(2-methylthio-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine dihydrochloride

5-(4-(4-Benzyloxy-phenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde (100 mg) and (methylthio)ethylamine (80 mg) in dichloromethane (5 ml) were reacted together as in Procedure D. Purification using column chromatography, followed by conversion to the hydrochloride salt gave a yellow solid (61 mg). m/z 497 $(M+1)^+$.

(6-Chloropyrido[3,4-d]pyrimidin-4-yl)-(4-(4-fluorobenzyloxy)-phenyl)-amine

4,6-Dichloro-pyrido[3,4-d]pyrimidine (1 g) and 4-(4-fluorobenzyloxy)aniline (1.08 g) in acetonitrile (70 ml) were reacted together as in Procedure A. The product was collected by filtration as a yellow solid (1.83 g); m/z 381 $(M+1)^+$.

(6-(5-(1,3-Dioxolan-2-yl)-furan-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-(4-(4-fluorobenzyloxy)-phenyl)-amine

(6-Chloropyrido[3,4-d]pyrimidin-4-yl)-(4-(4-fluorobenzyloxy)-phenyl)-amine (1.82 g) and 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)-furan (3.75 g) in dioxan (40 ml) were reacted together as in Procedure B. The mixture was evaporated and the residue suspended in dichloromethane. This was then filtered through celite and the solvent evaporated. The gummy residue was then triturated with hexane giving a beige solid (1.21 g); m/z 485 $(M+1)^+$.

5-(4-(4-(4-Fluorobenzyloxy)-phenylamino)-pyrido [3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde

(6-(5-(1,3-Dioxolan-2-yl)-furan-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-(4-(4-fluorobenzyloxy)-phenyl)-amine (500 mg) was treated with acid as in Procedure C. The product was collected by filtration as a red solid (330 mg); m/z 441 $(M+1)^+$.

(4-(4-Fluorobenzyloxy)-phenyl)-(6-(5-(2-(methylthio)-ethylaminomethyl)-furan-2-yl)-pyrido [3,4-d]pyrimidin-4-yl)-amine

5-(4-(4-(4-Fluorobenzyloxy)-phenyl)-pyrido[3,4-d] pyrimidin-6-yl)-furan-2-carbaldehyde (110 mg) and (methylthio)ethylamine (0.06 ml) in dichloromethane (5 ml) were reacted together as in Procedure D. Purification using a Bond Elut™ cartridge gave a yellow oil (52 mg); m/z 516 $(M+1)^+$.

(6-Chloropyrido[3,4-d]pyrimidin-4-yl)-(4-(3-fluorobenzyloxy)-phenyl)-amine

4,6-Dichloro-pyrido[3,4-d]pyrimidine (1 g) and 4-(3-fluorobenzyloxy)aniline (1.08 g) in acetonitrile (70 ml) were reacted together as in Procedure A. The product was collected by filtration as a yellow solid (1.86 g); m/z 381 $(M+1)^+$.

(6-(5-(1,3-Dioxolan-2-yl)-furan-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-(4-(3-fluorobenzyloxy)-phenyl)-amine

(6-Chloropyrido[3,4-d]pyrimidin-4-yl)-(4-(3-fluorobenzyloxy)-phenyl)-amine (1.85 g) and 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)-furan (3.82 g) in dioxan (40 ml) were reacted together as in Procedure B. The mixture was evaporated and the residue suspended in dichloromethane. This was then filtered through Celite® and the solvent evaporated. The gummy residue was then triturated with hexane giving a beige solid (1.74 g); m/z 485 $(M+1)^+$.

5-(4-(4-(3-Fluorobenzyloxy)-phenylamino)-pyrido [3,4-d]pyrimidin-6-yl)-furan-3-carbaldehyde

(6-Chloropyrido[3,4-d]pyrimidin-4-yl)-(4-(3-fluorobenzyloxy)-phenyl)-amine (1 g) and 5-(tributylstannyl)-furan-3-carbaldehyde (J. Org. Chem. (1992), 57(11), 3126–31) (1.84 g) in dioxan (35 ml) were reacted together as in Procedure B. The solvent was evaporated and the residue suspended in dichloromethane. The mixture was filtered through Celite® and then evaporated. The residue was triturated with hexane giving a beige solid (1 g); m/z 441 $(M+1)^+$.

5-(4-(4-(3-Fluorobenzyloxy)-phenylamino)-pyrido [3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde

(6-(5-(1,3-Dioxolan-2-yl)-furan-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-(4-(3-fluorobenzyloxy)-phenyl)-amine (500 mg) was treated with acid as in Procedure C. The product was collected by filtration as a beige solid (251 mg); ml/z 441 $(M+1)^+$.

(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-(2-(methylthio)-ethylaminomethyl)-furan-2-yl)-pyrido [3,4-d]pyrimidin-4-yl)-amine

(5-(4-(4-(3-Fluorobenzyloxy)-phenyl)-pyrido[3,4-d] pyrimidin-6-yl)-furan-2-carbaldehyde (125 mg) and (methylthio)ethylamine (0.08 ml) in dichloromethane (5 ml) were reacted together as in Procedure D. Purification using a Bond Elut™ cartridge gave a yellow oil (80 mg); m/z 516 $(M+1)^+$.

(4-Benzenesulphonyl-phenyl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine

Prepared according to Procedure A from 4-benzenesulphonylaniline (*Helv. Chim. Acta.*, 1983, 66 (4), 1046) and 4,6-dichloropyrido[3,4-d]pyrimidine; δH [$^2H_6$]-DMSO 9.09 (1H, s), 8.80–8.88 (2H, m), 8.19 (2H, d), 7.94–8.09 (4H, m), 7.53–7.20 (3H, m); m/z $(M+1)^+$397.

(4-Benzenesulphonyl-phenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine

(4-Benzenesulphonyl-phenyl)-(6-chloro-pyrido[3,4-d] pyrimidin-4-yl)-amine (3.67 g) and 5-(1,3-dioxolan-2-yl)-2-

(tributylstannyl)-furan (6.9 g) were reacted together in dioxan (100 ml) as in Procedure B. Purification by column chromatography gave a cream solid (2.59 g); δH [$^2H_6$] DMSO 10.6 (1H, s) 9.26 (1H, s) 8.82 (1H, s) 8.78 (1H, s) 8.25 (2H, d) 8.0–8.3 (4H, d+m) 7.65–7.8 (3H, m) 7.21 (1H, d) 6.82 (1H, d) 6.09 (1H, s) 4.0–4.2 (4H, m); m/z 501 $(M+1)^+$.

5-(4-(4-Benzenesulphonyl-phenylamino)-pyrido[3,4-d]pyrimidin-6-yl)furan-2-carbaldehyde hydrochloride

(4-Benzenesulphonyl-phenyl)-(6-(5-(1,3-dioxolan-2-yl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine (2.59 g) was treated with acid in tetrahydrofuran (70 ml) as in Procedure C. The compound was obtained as a yellow solid after filtration (1.57 g); δH [$^2H_6$]DMSO 9.7 (1H, s) 9.26 (1H, s) 9.11 (1H, s) 8.82 (1H, s) 8.19 (1H, s) 8.15 (1H, s) 7.95–8.03 (4H, m) 7.75 (1H, d) 7.58–7.7 (3H, m) 7.49 (1H, s); m/z 457 $(M+1)^+$.

(4-Benzenesulphonyl-phenyl)-(6-(5-((2-methylthio-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d] pyrimidin-4-yl)-amine dihydrochloride

5-(4-((4-Benzenesulphonyl-phenyl)amino)-pyrido[3,4-d] pyrimidin-6-yl)-furan-2-carbaldehyde (250 mg) and (methylthio)ethylamine (185 mg)) in dichloromethane (5 ml) were reacted together as in Procedure D. Purification using a Bond Elut™ cartridge, gave a yellow solid (245 mg), 70 mg of which was converted to the hydrochloride salt, (yellow solid, 68 mg); m/z 532 $(M+1)^+$.

(4-Benzyloxy-phenyl)-(6-(3-(1,3-dioxolan-2-yl)-phenyl)-pyrido[3,4-d]pyrimidin-4-yl)-amine

(4-Benzyloxy-phenyl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine (1.4 g) and 3-(1,3-dioxolan-2-yl)-phenyl-tributylstannane (3.08 g) [A. Lee and W-C. Dai, Tetrahedron (1997), 53(3), 859–868] in dioxan (30 ml) were reacted together as in Procedure B. The mixture was evaporated and the residue suspended in dichloromethane. This was then filtered through celite and the solvent evaporated. The gummy residue was then triturated with hexane giving a beige solid. This material was further purified by column chromatography, giving a brown foam (252 mg); m/z 477 $(M+1)^+$.

3-(4-((4-Benzyloxy-phenyl)-amino)-pyrido[3,4-d] pyrimidin-6-yl)-benzaldehyde

(4-(4-Benzyloxy-phenyl)-6-(3-(1,3-dioxolan-2-yl)-phenyl)-pyrido[3,4-d]pyrimidin-4-yl)-amine (250 mg) was treated with acid as in Procedure C. The product was isolated by filtration as a brown solid (115 mg); m/z 433 $(M+1)^+$.

4-(4-(4-Benzyloxy-phenyl)-amino)-quinazolin-6-yl)-thiazol-2-carbaldehyde

(4-Benzyloxy-phenyl)-(6-iodo-quinazolin-4-yl)-amine (2 g) and 4-(tributylstannyl)-thiazol-2-carbaldehyde (3.28 g) in dioxan (25 ml) were reacted together as in Procedure B. The mixture was evaporated and the residue purified using column chromatography, giving a yellow solid (849 mg); m/z 439 $(M+1)^+$.

Other suitable intermediates prepared by analogous methods to those described above are:

(4-Benzyloxy-3-chlorophenyl)-6-chloro-pyrido[3,4-d] pyrimidin-4-yl)-amine;

(4-(3-Fluoro-benzyloxy)-3-chlorophenyl)-6-chloro-pyrido [3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-3-trifluoromethylphenyl)-6-chloro-pyrido[3, 4-d]pyrimidin-4-yl)-amine;

(4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl)-6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-3-bromophenyl)-6-chloro-pyrido[3,4-d] pyrimidin-4-yl)-amine;

(4-(3-Fluoro-benzyloxy-3-bromophenyl)-6-chloro-pyrido [3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-3-iodophenyl)-6-chloro-pyrido[3,4-d] pyrimidin-4-yl)-amine;

(4-(3-Fluoro-benzyloxy-3-iodophenyl)-6-(chloro-pyrido[3, 4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-3-fluorophenyl)-6-chloro-pyrido[3,4-d] pyrimidin-4-yl)-amine;

(4-(3-Fluoro-benzyloxy-3-fluorophenyl)-6-chloro-pyrido[3, 4-d]pyrimidin-4-yl)-amine;

5-((4-Benzyloxy-3-chlorophenylamino)-pyrido[3,4-d] pyrimidin-6-yl)-furan-2-carbaldehyde;

5-((4-(3-Fluoro-benzyloxy)-3-chlorophenylamino)-pyrido [3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;

5-((4-Benzyloxy-3-trifluoromethylphenylamino)-pyrido[3, 4-d]6-yl)-furan-2-carbaldehyde;

5-((4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;

5-((4-Benzyloxy-3-bromophenylamino)-pyrido[3,4-d] pyrimidin-6-yl)-furan-2-carbaldehyde;

5-((4-(3-Fluoro-benzyloxy-3-bromophenylamino)-pyrido [3,4-d]6-yl)-furan-2-carbaldehyde;

5-((4-Benzyloxy-3-iodophenylamino)-pyrido[3,4-d] pyrimidin-6-yl)-furan-2-carbaldehyde;

5-((4-(3-Fluoro-benzyloxy-3-iodophenylamino)-pyrido[3, 4-d]6-yl)-furan-2-carbaldehyde;

5-((4-Benzyloxy-3-fluorophenylamino)-pyrido[3,4-d] pyrimidin-6-yl)-furan-2-carboxaldehyde;

5-((4-(3-Fluoro-benzyloxy-3-fluorophenylamino)-pyrido[3, 4-d]6-yl)-furan-2-carbaldehyde;

N-[4-(benzyloxy)-3-chlorophenyl]-7-fluoro-6-chloro-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-fluoro-6-chloro-4-quinazolinamine

N-[4-Benzyloxy-3-trifluoromethylphenyl]-7-fluoro-6-chloro-4-quinazolinamine

N-[4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl]-7-fluoro-6-chloro-4-quinazolinamine;

N-[4-Benzyloxy-3-bromophenyl]-7-fluoro-6-chloro-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy-3-bromophenyl]-7-fluoro-6-chloro-4-quinazolinamine;

N-[4-Benzyloxy-3-iodophenyl]-7-fluoro-6-chloro-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy-3-iodophenyl]-7-fluoro-6-chloro-4-quinazolinamine;

N-[4-Benzyloxy-3-fluorophenyl]-7-fluoro-6-chloro-4-quinazolinamine;

N-[4-(3-Fluoro-benzyloxy-3-fluorophenyl]-7-fluoro-6-chloro-4-quinazolinamine;

N-[1-(3-fluorobenzyl-1H-indazol-5-yl]-7-fluoro-6-chloro-4-quinazolinamine;

5-(4-[4-(Benzyloxy)-3-chlorophenylamino]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;

5-(4-[4-(3-Fluoro-benzyloxy)-3-chlorophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;

5-(4-[4-Benzyloxy-3-trifluoromethylphenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;

5-(4-[4-(3-Fluoro-benzyloxy)-3-trifluoromethylphenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;

5-(4-[4-Benzyloxy-3-bromophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;

5-(4-[4-(3-Fluoro-benzyloxy-3-bromophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;

5-(4-[4-Benzyloxy-3-iodophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;

5-[4-(3-Fluoro-benzyloxy-3-iodophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;

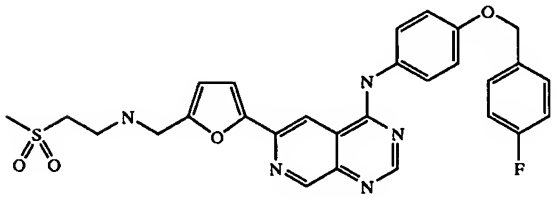
5-[4-Benzyloxy-3-fluorophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde

5-[4-(3-Fluoro-benzyloxy-3-fluorophenyl]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;

5-(4-[1-(3-Fluorobenzyl-1H-indazol-5-ylamino]-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde;

EXAMPLES

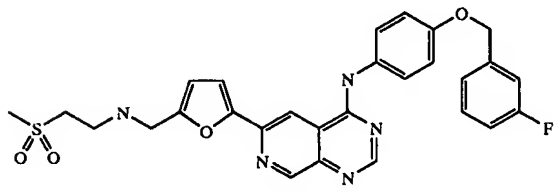
Example 1



(4-(4-Fluorobenzyloxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine Dihydrochloride

(4-(4-Fluorobenzyloxy)-phenyl)-(6-(5-(2-(methylthio)-ethylaminomethyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine (52 mg) in methanol (9 ml) and water (3 ml) was treated with Oxone™ (99 mg) at room temperature for 2 days. The mixture was then partitioned between aqueous sodium carbonate solution and dichloromethane. The dried organic phase was evaporated and the residue purified by Bond Elut™ cartridge, followed by conversion to the hydrochloride salt, giving a yellow solid (31 mg); δH [$^2H_6$]DMSO 9.9 (1H, bs) 9.25 (1H, s) 8.8 (1H, s) 7.9 (2H, d) 7.5–7.6 (2H, m) 7.1–7.3 (5H, m) 6.9 (1H, d) 5.2 (2H, s) 4.5 (2H, s) 3.6–3.8 (4H, m) 3.2 (3H, s); m/z 548 $(M+1)^+$.

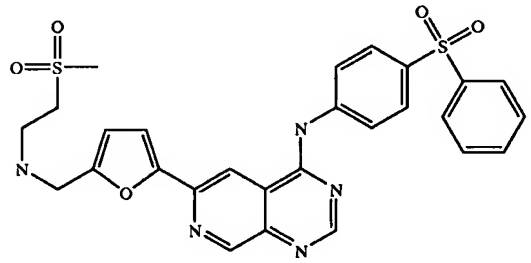
Example 2



(4-(3-Fluorobenzyl oxy)-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino) methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine Dihydrochloride

(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-(2-(methylthio)-ethylaminomethyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine (80 mg) in methanol (9 ml) and water (3 ml) was treated with Oxone™ (153 mg) at room temperature for 2 days. The mixture was then partitioned between aqueous sodium carbonate solution and dichloromethane. The dried organic phase was evaporated and the residue purified by Bond Elut™ cartridge, followed by conversion to the hydrochloride salt, giving a yellow solid (69 mg); δH [$^2H_6$]DMSO 9.8 (1H, bs) 9.4 (1H, s) 9.3 (1H, s) 8.7 (1H, s) 7.8 (2H, d) 7.3–7.4 (2H, m) 7.0–7.3 (5H, m) 6.8 (1H, d) 5.3 (2H, s) 4.4 (2H, s) 3.5–3.7 (4H, m) 3.1 (3H, s); m/z 548 $(M+1)^+$.

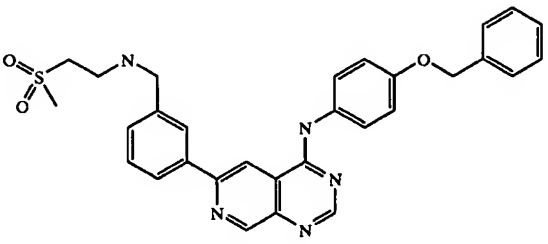
Example 3



(4-Benzenesulphonyl-phenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine Dihydrochloride

(4-Benzenesulphonyl-phenyl)-(6-(5-((2-methylthio-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine (162 mg) in methanol (20 ml) and water (10 ml) was treated with Oxone™ (345 mg) at room temperature for 18h. The mixture was then evaporated and the residue purified by Bond Elut™ cartridge, followed by conversion to the hydrochloride salt, giving a yellow solid (55 mg); δH [$^2H_6$]DMSO 9.8 (1H, bs) 9.3 (1H, s) 9.2 (1H, s) 8.8 (1H, s) 8.3 (2H, d) 7.9–8.0 (4H, m) 7.6–7.7 (3H, m) 7.2 (1H, d) 6.8 (1H, d) 4.4 (2H, s) 3.3–3.7 (4H, m) 3.1 (3H, s); m/z 564 $(M+1)^+$.

Example 4

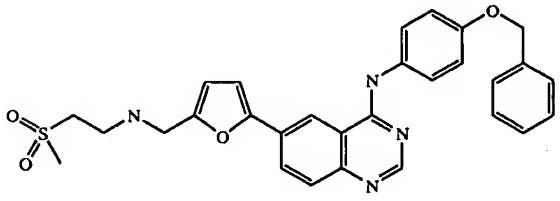


(4-Benzyloxy-phenyl)-(6-(3-((2-methanesulphonyl-ethylamino)-methyl)-phenyl)-pyrido[3,4-d] pyrimidin-4-yl)-amine dihydrochloride.

3-((4-(4-Benzyloxy-phenyl)-amino)-pyrido[3,4-d] pyrimidin-6-yl)-benzaldehyde (106 mg) and 2-methanesulphonyl-ethylamine (111 mg) in dichloromethane (5 ml) were reacted together as in Procedure D. Purification using column chromatography, followed by

conversion to the hydrochloride salt, gave a yellow solid (66 mg); δH [$^2H_6$]DMSO 9.6 (2H, bs) 9.3 (1H, s) 9.2 (1H, s) 8.65 (1H, s) 8.55 (1H, s) 8.3 (1H, m) 7.7–7.8 (2H, m) 7.6 (2H, m) 7.25–7.45 (4H, m) 7.0 (2H, d) 5.1 (2H, s) 4.3 (2H, s) 3.2–3.8 (4H, m) 3.1 (3H, s). m/z 540 $(M+1)^+$.

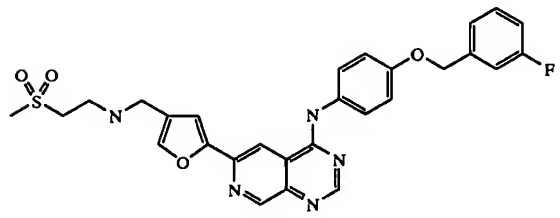
Example 5



(4-Benzyloxyphenyl)-(6-(5-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-quinazolin-4-yl)-amine dihydrochloride

5-((4-(4-Benzyloxyphenyl)-amino)-quinazolin-6-yl)-furan-2-carbaldehyde (200 mg) and 2-methanesulphonyl-ethylamine (215 mg) in dichloromethane (10 ml) were reacted together as in Procedure D. Purification using column chromatography, followed by conversion to the hydrochloride salt, gave a yellow solid (121 mg); δH [$^2H_6$]DMSO 9.7 (1H, s) 8.9 (1H, s) 8.4 (1H, d) 8.0 (1H, d) 7.75 (2H, d) 7.3–7.5 (7H, m) 7.1 (2H, d) 6.85 (1H, d) 5.2 (2H, s) 4.4 (2H, s) 3.2–3.7 (4H, m) 3.1 (3H, s); m/z 529$(M+1)^+$.

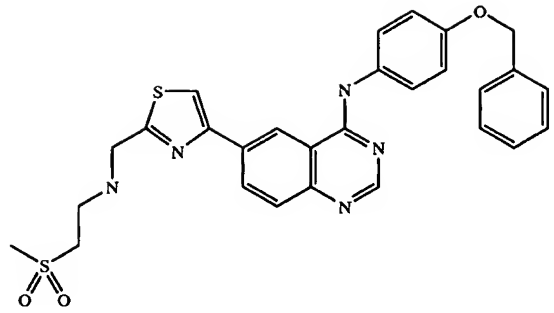
Example 6



(4-(3-Fluorobenzyloxy)-phenyl)-(6-(4-((2-methanesulphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine dihydrochloride

5-(4-(4-(3-Fluorobenzyloxy)-phenyl)-pyrido[3,4-d] pyrimidin-6-yl)-furan-3-carbaldehyde (300 mg) and 2-methanesulphonyl-ethylamine (335 mg) in dichloromethane (15 ml) were reacted together as in Procedure D. Purification using a Bond Elut™ cartridge, followed by conversion to the hydrochloride salt, gave a yellow solid (110 mg); δH [$^2H_6$]DMSO 9.8 (2H, br) 9.3 (1H, s) 9.0 (1H, s) 8.8 (1H, s) 8.2 (1H, s) 8.0 (1H, s) 7.1–7.8 (7H, m) 7.0 (1H, s) 5.2 (2H, s) 4.1–4.3 (4H, brm) 3.3–3.5 (2H, bs) (hidden under H_2O peak) 3.2 (3H, s); m/z 548$(M+1)^+$.

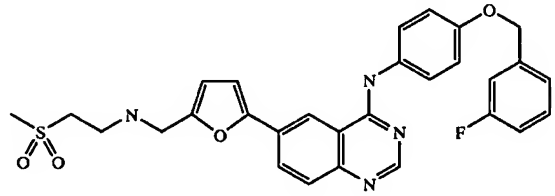
Example 7



(4-Benzyloxy-phenyl)-(6-(2-((2-methanesulphonyl-ethylamino)-methyl)-thiazol-4-yl)-quinazolin-4-yl)-amine dihydrochloride

4-(4-(4-Benzyloxy-phenyl)-amino)-quinazolin-6-yl)-thiazol-2-carbaldehyde (70 mg) and 2-methanesulphonyl-ethylamine (79 mg) in dichloromethane (10 ml) were reacted together as in Procedure D. Purification using a Bond Elut™ cartridge, followed by conversion to the hydrochloride salt, gave a yellow solid (59 mg); δH [$^2H_6$]DMSO 12.3 (1H, s) 10.0 (1H, s) 8.95 (1H, s) 8.8 (1H, s) 8.75 (1H, d) 7.4–7.6 (6H, m) 7.2 (2H, d) 5.25 (2H, s) 4.8 (2H, s) 3.6–3.8 (4H, m) 3.2 (3H, s); m/z 546$(M+1)^+$.

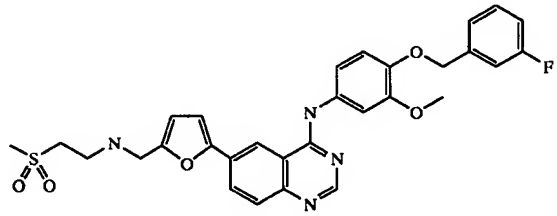
Example 8



N-{4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{4-(3-fluorobenzyloxy)anilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^1H NMR 400 MHz (DMSO-d6) 9.40 (s, 1H); 8.67 (s, 1H); 8.30 (d, 1H); 7.86 (d, 1H); 7.75 (d, 2H); 7.43 (m, 1H); 7.30–7.21 (m, 3H); 7.15 (m, 1H); 7.07 (d, 2H); 6.80 (d, 1H); 5.15 (s, 2H); 4.40 (s, 2H); 3.65 (m, 2H); 3.40 (m, 2H); 3.11 (s, 3H); MS m/z 547 (M+1).

Example 9

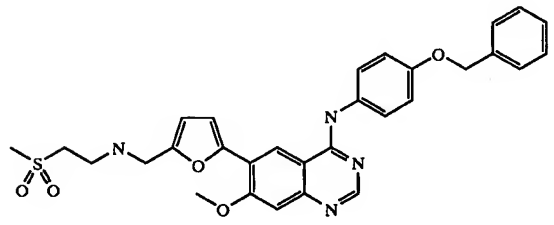


N-{14-[(3-fluorobenzyl)oxy]-3-methoxyphenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-methoxy-4-(3-fluorobenzyloxy)anilino}-6-quinazolinyl)-

furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 9.22 (s, 1H); 8.78 (s, 1H); 8.31 (d, 1H); 7.88 (d, 1H); 7.50–7.08 (m, 8H); 6.84 (d, 1H); 5.13 (s, 2H); 4.42 (s, 2H); 3.80 (s, 3H); 3.60 (m, 2H); 3.40 (m, 2H, obscured by water peak); 3.10 (s, 3H); MS m/z 577 (M+1).

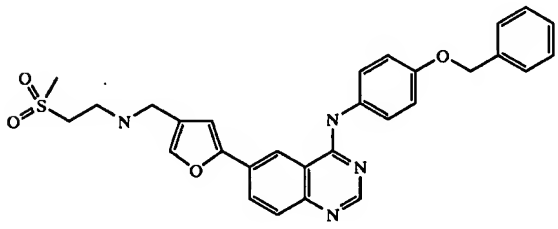
Example 10



N-[4-(benzyloxy)phenyl]-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared in a similar manner to Procedure D from 5-(4-(4-benzyloxy-phenylamino)-7-methoxy-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride(78 mg, 0.16 mmol), 2-methanesulphonylethylamine(33 mg, 0.27 mmol), acetic acid(15 mg, 0.25 mmol) and triethylamine(18 mg, 0.18 mmol) in 3 ml of 1,2-dichloroethane added to sodium triacetoxyborohydride(102 mg, 0.48 mmol) portionwise over a two day period. The reaction mixture was stirred four days and then partitioned between 10 ml of 0.5M $NaHCO_3$ solution and 50 ml of ethyl acetate. The organic solution was dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel with methanol/methylene chloride(1:49 to 2:48). The resulting solid was crystallized from a small volume of ethyl acetate, suspended in ether and filtered to give 43 mg of product as a pale yellow solid. δ^1H NMR (400 MHz, DMSO-d_6) 9.78(s, 1H), 8.73(s, 1H), 8.42(s, 1H), 6.64(d, 2H), 7.47(m, 2H), 7.40(m, 2H), 7.33(m, 1H), 7.25(s, 1H), 7.04(d, 2H), 6.98(d, 1H), 6.46(d, 1H), 5.12(s, 2H), 4.04(s, 3H), 3.86(s, 2H), 3.28(t, 2H), 3.01 (s, 3H), 2.99(t, 2H). ESI-MS m/z 559(M+1).

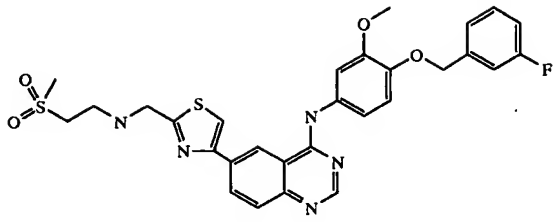
Example 11



N-[4-(benzyloxy)phenyl]-6-[4-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{4-benzyloxyanilino}-6-quinazolinyl)-furan-3-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}HNMR 400 MHz, d6DMSO 9.51 (bs, 2H), 9.11 (s, 1H), 8.79 (s, 1H), 8.29 (d, 1H), 8.06 (s, 1H), 7.90 (d, 1H), 7.60 (d, 2H), 7.5–7.3 (m, 5H), 7.11 (d, 2H), 5.14 (s, 2H), 4.14 bs, 2H), 3.6–3.5 (m, 3H), 3.12 (s, 3H); MS m/z 529 (M+1).

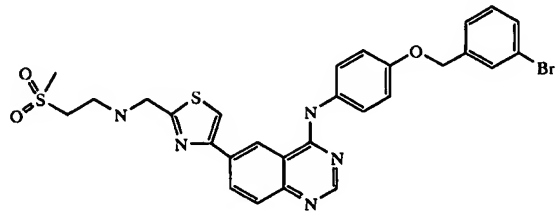
Example 12



N-{4-[(3-fluorobenzyl)oxy]-3-methoxyphenyl}-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-(4-(3-fluorobenzyloxy)-3-methoxypheny)quinazolin-4-ylamine (1 equiv), 2-ethoxyvinyl-tributylstannane (1-equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv) .^{1}H NMR 400 MHz (CD_3OD) 9.40 (s, 1H); 8.79 (s, 1H); 8.76 (d, 1H); 8.38 (s, 1H); 7.89 (d, 1H); 7.50 (s, 1H); 7.40 (t, 1H); 7.34 (m, 1H); 7.27 (d, 1H); 7.22 (d, 1H); 7.08 (d, 1H); 7.03 (t, 1H); 5.19 (s, 2H); 4.81 (s, 2H); 3.85 (m, 2H); 3.75 (m, 2H); 3.10 (s, 3H); MS m/z 594 $(M+1)^+$, 592 $(m-1)^-$.

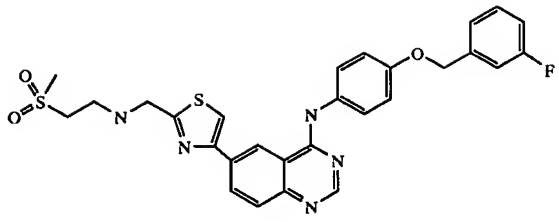
Example 13



N-{4-[(3-bromobenzyl)oxy]phenyl}-6-[2-{[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-(4-(3-bromobenzyloxy)-phenyl)quinazolin-4-ylamine (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). ^{1}H NMR 400 MHz (CD_3OD) 9.40 (s, 1H); 8.78 (d, 1H); 8.74 (d, 1H); 8.34 (s, 1H); 7.88 (d, 1H); 7.65 (d, 2H); 7.62 (s, 1H); 7.48 (d, 1H); 7.30 (d, 1H); 7.30 (m, 1H); 7.12 (d, 2H); 5.16 (s, 2H); 4.80 (s, 2H); 3.85 (m, 2H); 3.75 (m, 2H); 3.10 (s, 3H); MS m/z 624, 626 $(M+1)^+$, 622, 624 $(m-1)^-$.

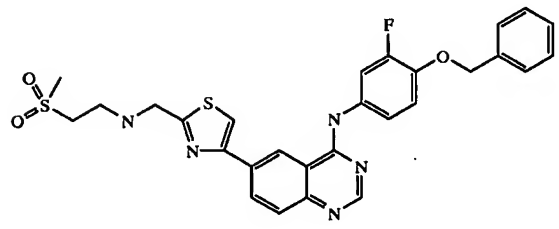
Example 14



N-{4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-{[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-(4-(3-fluorobenzyloxy)-phenyl)-quinazolin-4-ylamine and (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). ^{1}H NMR 400 MHz (CD_3OD) 9.44 (s, 1H); 8.79 (s, 1H); 8.76 (d, 1H); 8.37 (s, 1H); 7.90 (d, 1H); 7.74 (d, 1H); 7.53 (d, 1H); 7.46 (d, 2H); 7.38 (m, 2H); 7.32 (d, 1H); 7.24 (d, 1H); 5.21 (s, 2H); 4.82 (s, 2H); 3.85 (m, 2H); 3.77 (m, 2H); 3.11 (s, 3H); MS m/z 564 $(M+1)^+$, 562 $(m-1)^-$.

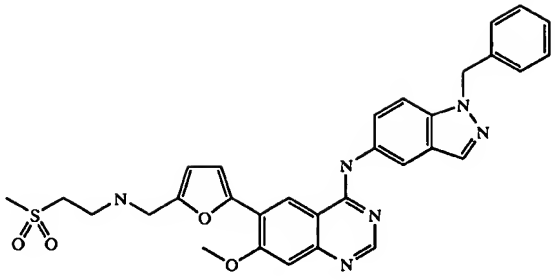
Example 15



N-[4-(benzyloxy)-3-fluorophenyl]-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-(4-benzyloxy)-3-fluorophenyl)quinazolin-4-ylamine and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). ^{1}H NMR 400 MHz (CD_3OD) 9.41 (s, 1H); 8.77 (d, 1H); 8.75 (s, 1H); 8.36 (s, 1H); 7.90 (d, 1H); 7.71 (d, 2H); 7.60 (m, 1H); 7.40 (m, 1H); 7.23 (m, 1H); 7.11 (d, 2H); 7.03 (m, 1H); 5.17 (s, 2H); 4.81 (s, 2H); 3.85 (m, 2H); 3.76 (m, 2H); 3.10 (s, 3H); MS m/z 564 $(M+1)^+$, 562 $(m-1)^-$.

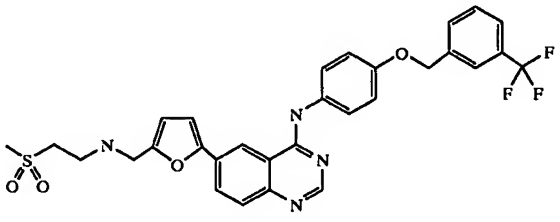
Example 16



N-(1-benzyl-1H-indazol-5-yl)-7-methoxy-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{4-(1-benzyl-1H-indazol-5-yl)-7-methoxy-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). δ^1H NMR (400 MHz, DMSO-d_6) 9.94(s, 1H), 8.76(s, 1H), 8.43(s, 1H), 8.13(d, 1H), 8.12(s, 1H), 7.70(d, 1H), 7.66(m, 1H), 7.31 (m, 2H), 7.25(m, 4H), 7.00(d, 1H), 6.46(d, 1H), 5.67(s, 2H), 4.05(s, 3H), 3.85(s, 2H), 3.27(t, 2H), 3.00(s, 3H), 2.98(t, 2H); ESI-MS m/z 583(M+1).

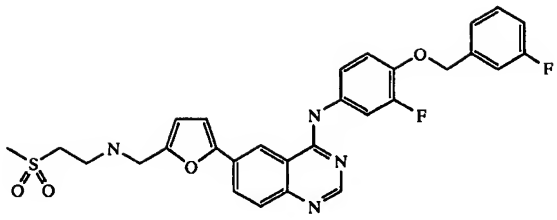
Example 17



6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-N-(4-{[3-(trifluoromethyl) benzyl] oxy}phenyl)-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{4-(3-trifluoromethylbenzyloxy)anilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 300 MHz (DMSO-d6) 11.63 (bs, 1H); 9.88 (bs, 1H); 9.59 (bs, 1H); 8.88 (s, 1H); 8.43 (d, 1H); 7.97 (d, 1H); 7.90–7.67 (m, 6H); 7.34 (d, 1H); 7.19 (d, 2H); 6.89 (d, 1H); 5.30 (s, 2H); 4.45 (s, 2H); 3. 78 (m, 2H); 3.45 (m, 2H, obscured by water peak); 3.19 (s, 3H); MS m/z 597 (M+1).

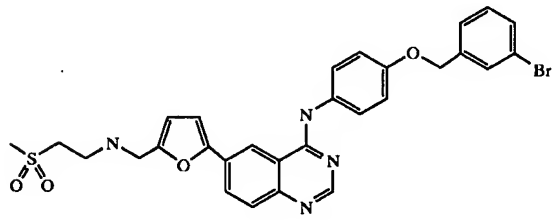
Example 18



N-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-fluoro-4-(3-fluorobenzyloxy)anilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 9.61 (bs, 2H); 9.28 (bs, 1H); 8.80 (s, 1H); 8.34 (d, 1H); 7.87 (m, 2H); 7.59 (d, 1H); 7.44 (m, 1H); 7.2–7.38 (m, 4H); 7.18 (m, 1H); 6.83 (s, 1H); 5.25 (s, 2H); 4.42 (s, 2H); 3.60 (m, 2H); 3.45 (m, 2H, obscured by water peak); 3.16 (s, 3H); MS m/z 565 (M+1).

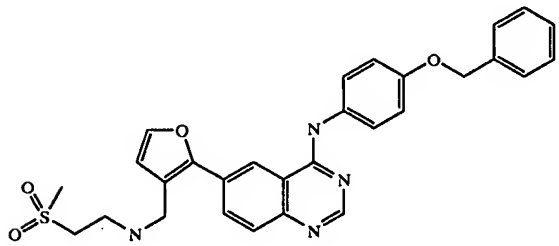
Example 19



N-{4-[(3-bromobenzyl)oxy]phenyl}-6-[5-(J[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-bromo-4-benzyloxyanilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 11.78 (bs, 1H); 9.65 (bs, 1H); 9.39 (bs, 1H); 8.78 (s, 1H); 8.37 (d, 1H); 7.90 (d, 1H); 7.66 (m, 3H); 7.53 (d, 1H); 7.42 (d, 1H); 7.38 (m, 1H); 7.22 (s, 1H); 7.18 (d, 2); 6.82 (d, 1H); 5.18 (s, 2H); 4.41 (s, 2H); 3.62 (m, 2H); 3.44 (m, 2H, obscured by water peak); 3.10 (s, 3H); MS m/z 606, 608 (M+1).

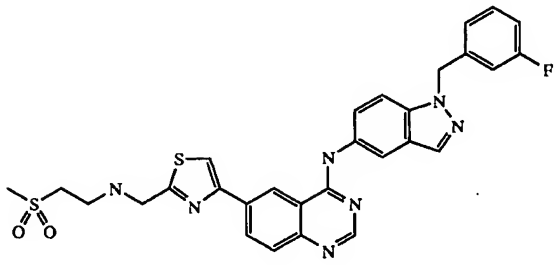
Example 20



N-[4-(benzyloxy)phenyl]-6-[3-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-(4-benzyloxyanilino)-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine(1 equiv). ^{1}HNMR 400 MHz,(d6DMSO) 9.46(brs, 1H), 8.94 (s, 1H), 8.7 (s, 1H), 8.16 (d, 1H), 7.96 (s, 1H), 7.88 (d, 1H), 7.67 (d, 2H), 7.5–7.2 (m, 5H), 7.07 (d, 2H), 6.93 (s, 1H), 5.12 (s, 2H), 4.38 (brs, 2H), 3.59 (m, 2H), 3.46 (brs, 2H), 3.09 (s, 3H); MS m/z 529 (M+1)

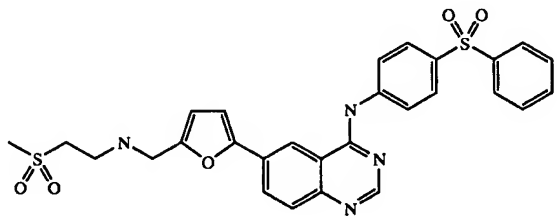
Example 21



N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]-6-[2-{[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-(4-(3-fluorobenzyl)-1H-indazol-5-yl)quinazolin-4-ylamine (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). ^{1}H NMR (d_4 MeOH) d 9.44 (s, 1H), 8.76 (m, 2H), 8.36 (s, 1H), 8.18 (s, 1H), 8.15, (s, 1H), 7.92 (d, 1H), 7.75 (m, 2H), 7.34 (m, 1H), 7.04 (m, 2H), 6.92 (d, 1H), 5.71 (s, 2H), 4.80 (s, 2H), 3.82 (m, 2H), 3.74 (m, 2H), 3.08 (s, 3H); MS m/z 588 (M+H+)

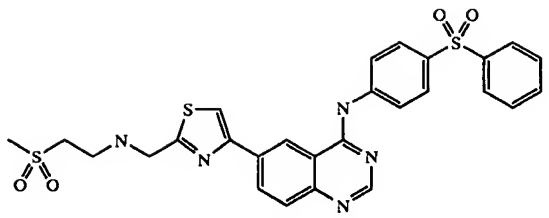
Example 22



6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-N-[4-(benzenesulphonyl)phenyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{4-(benzenesulphonyl)phenyl}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR (DMSO-d6) 10.27 (s, 1H), 8.78 (s, 1H), 8.65 (s, 1H), 8.18–8.22 (m, 3H), 7.97–8.01 (m, 4H), 7.86 (d, 1H), 7.62–7.72 (m, 3H), 7.10 (d, 1H), 6.51 (d, 1H), 3.84 (s, 1H), 3.28 (t, 2H), 3.03 (s, 3H), 2.99 (t, 2H); m/z $(M+1)^+$563.

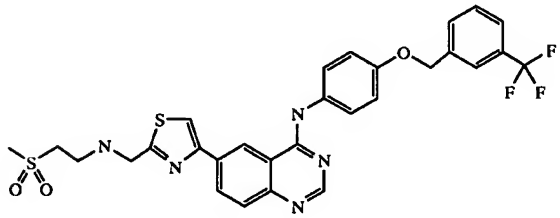
Example 23



6-[2-{[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-N-[4-(benzenesulphonyl)phenyl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-(4-(benzenesulphonyl)-phenyl)-quinazolin-4-ylamine (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 9.80 (s, 1H); 8.87 (s, 1H); 8.65 (s, 1H); 8.64 (s, 1H); 8.17 (s, 1H); 8.03 (s, 1H); 7.98 (m, 2H); 7.66 (m, 5H); 4.73 (s, 2H); 3.68 (m, 2H); 3.55 (m, 2H); 3.12 (s, 3H); MS m/z 580 $(M+1)^+$, 578 $(m-1)^-$.

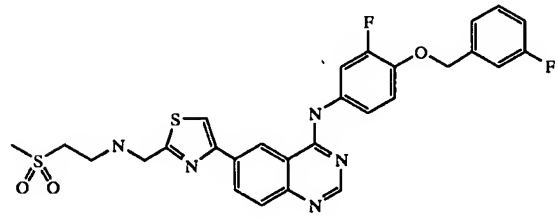
Example 24



6-[2-{[2-(methanesulphonyl)ethyl]amino}methyl)-1.3-thiazol-4-yl]-N-(4-{[3-(trifluoromethy)benzyl] oxy}phenyl)-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-(4-(3-trifluoromethylbenzyloxy)-phenyl)quinazolin-4-ylamine (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). ^{1}H NMR 400 MHz (CD_3OD) 9.40 (s, 1H); 8.75 (d, 1H); 8.73 (s, 1H); 8.35 (s, 1H); 7.89 (d, 1H); 7.77 (s, 1H); 7.73 (m, 1H); 7.61 (m, 3H); 7.52 (m, 1H); 7.14 (d, 2H); 5.24 (s, 2H); 4.82 (s, 2H); 3.85 (m, 2H); 3.76 (m, 2H); 3.10 (s, 3H); MS m/z 614 $(M+1)^+$, 612 $(m-1)^-$.

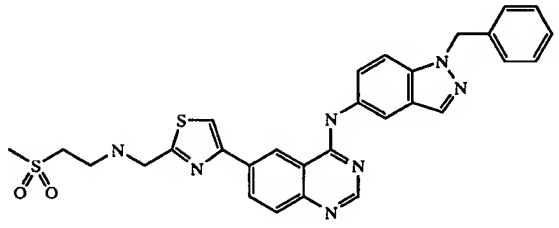
Example 25



N-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-{[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-4-(1-benzyl-1H-indazol-5-yl)-quinazolin-4-ylamine (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). ^{1}H NMR 400 MHz (CD_3OD) 9.28 (s, 1H); 8.78 (s, 1H); 8.74 (d, 1H); 8.31 (s, 1H); 7.90 (d, 1H); 7.74 (d, 1H); 7.63 (m, 1H); 7.54 (m, 1H); 7.49 (m, 1H); 7.37 (m, 1H); 7.25 (m, 2H); 7.05 (m, 1H); 5.24 (s, 2H); 4.77 (s, 2H); 3.81 (m, 2H); 3.72 (m, 2H); 3.10 (s, 3H); MS m/z 582 $(M+1)^+$, 580 $(m-1)^-$

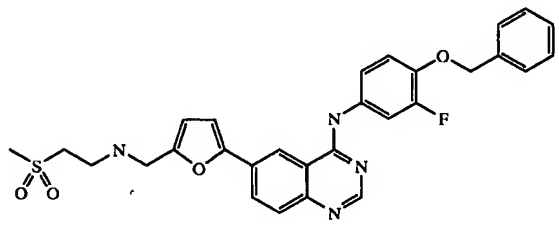
Example 26



N-(1-benzyl-1H-indazol-5-yl)-6-[2-({[2-(methanesulphonyl)ethyl]amino}methyl)-1,3-thiazol-4-yl]-4-quinazolinamine

Prepared according to Procedure F from 6-iodo-4-(1-benzyl-1H-indazol-5-yl)-quinazolin-4-ylamine (1 equiv), 2-ethoxyvinyl-tributylstannane (1 equiv), N-bromosuccinimide (1 equiv) and N-(trifluoroacetyl)-N-(methanesulphonylethyl)-aminomethylthioamide (1 equiv). δ^1H NMR (d_4 MeOH) 9.37 (s, 1H), 8.74 (m, 2H), 8.33 (s, 1H), 8.17 (s, 1H), 8.14, (s, 1H), 7.90 (d, 1H), 7.70 (m, 2H), 7.22 (m, 5H), 5.69 (s, 2H), 4.78 (s, 2H), 3.81 (m, 2H), 3.74 (m, 2H), 3.09 (s, 3H); MS m/z 570 $(M+H^+)$.

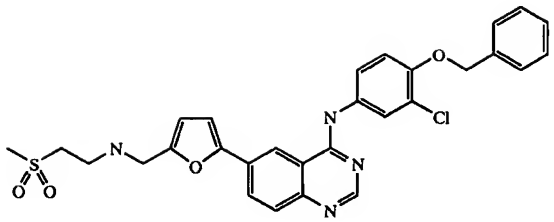
Example 27



N-(3-Fluoro-4-benzyloxyphenyl)-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-fluoro-4-benzyloxyanilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 8.83 (s, 1H); 8.35 (d, 1H); 7.89 (d, 1H); 7.83 (d, 1H); 7.59 (d, 1H); 7.48–7.31 (m, 7H); 7.26 (s, 1H); 6.83 (d, 1H); 5.21 (s, 2H); 4.42 (s, 2H); 3.60 (m, 2H); 3.44 (m, 2H, obscured by water peak); 3.12 (s, 3H); MS m/z 547 $(M+H^+)$.

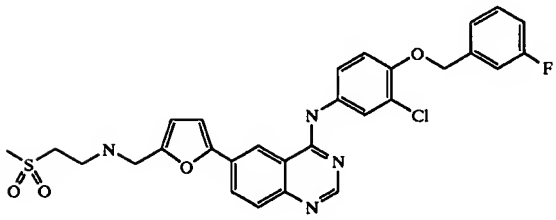
Example 28



N-(3-Chloro-4-benzyloxyphenyl)-6-[5-{[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-chloro-4-benzyloxyanilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 9.71 (bs, 2H); 9.45 (bs, 1H); 8.86 (s, 1H); 8.36 (d, 1H); 7.98 (d, 1H); 7.90 (d, 1H); 7.74 (d, 1H); 7.49–7.44 (m, 2H); 7.40 (m, 2H); 7.35–7.30 (m, 2H); 7.28 (d, 1H); 6.83 (d, 1H); 5.25 (s, 2H); 4.42 (s, 2H); 3.62 (m, 2H); 3.44 (m, 2H); 3.12 (s, 3H); MS m/z 563 ($M+H^+$).

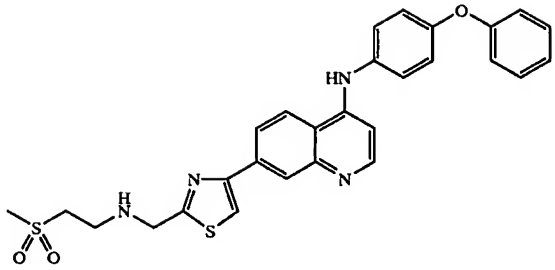
Example 29



N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-{3-chloro-4-(3-fluorobenzyloxy)-anilino}-6-quinazolinyl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR 400 MHz (DMSO-d6) 9.60 (bs, 1H); 9.32 (bs, 1H); 8.82 (bs, 1H); 8.34 (d, 1H); 8.0 (s, 1H); 7.88 (d, 1H); 7.74 (d, 1H); 7.45 (m, 1H); 7.34–7.23 (m, 4H); 7.17 (m, 1H); 6.83 (d, 1H); 5.27 (s, 2H); 4.42 (s, 2H); 3.59 (m, 2H); 3.40 (m, 2H, obscured by waterpeak); 3.12 (s, 3H); MS m/z 581 ($M+H^+$).

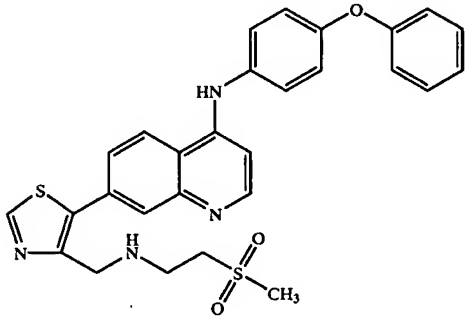
Example 30



(4-Phenoxyphenyl)-(7-(2-(2-methanesulphonyl) ethylaminomethyl)thiazol-4-yl)-quinolin-4-yl)amine

A suspension of (4-(4-(4-phenoxy)anilino)-quinolin-7-yl) thiazole-2-carbaldehyde (0.05 g, 0.14 mmol), sodium triacetoxyborohydride (0.1 2 g, 0.56 mmol), methanesulphonyl-ethylamine (0.15 g, 1.2 mmol) and powdered 3 A molecular sieves in dichloromethane (6 ml) and glacial acetic acid (1 ml) was stirred at room temperature (21° C.) overnight (18 hrs) according to Procedure D. The crude reaction mixture was filtered through a SPE column (SCX resin, 5 g, 25 ml), sequentially washed with methanol (2×10 ml) and 10% ammonia in methanol (3×10 ml) and the product isolated as a pale yellow gum. Trituration with water (5 ml) and drying of the resultant solid over phosphorus pentoxide at 60° C. under vacuum for 5 hrs yielded the purified product as a pale yellow solid (0.031 g, 49%); δH [$^2H_6$] DMSO 8.80(1H, s), 8.25(3H, m), 8.10(1H, s), 7.90(1H, d), 7.20(4H, 2d), 6.85 (5H, m), 6.60(1H, d), 3.95(2H, d), 2.90(7H, m); m/z 531 $(M+1)^+$.

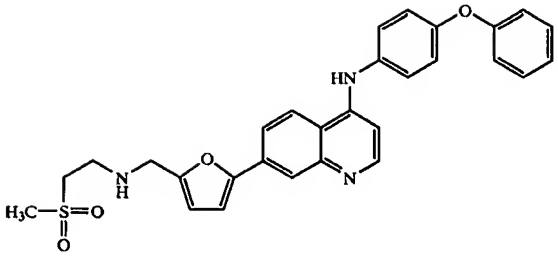
Example 31



(4-Phenoxyphenyl)-(7-(4-(2-methanesulphonyl) ethylaminomethyl)thiazol-5-yl)-quinolin-4-yl)amine

4-(4-Phenoxyanilino) 7-(4-formyl thiazol-5-yl) quinoline (50 mg, 0.118 mmol), methanesulphonylethylamine (50 mg) and molecular seives (4A, 2 large spatula tips) were stirred in a mixture of dichloromethane (6 ml) and acetic acid (1 ml) at room temperature for 2 hr (Procedure D). Sodium triacetoxyborohydride (0.12 g, 0.567 mmol) was then added and the reaction was stirred at room temp for 18 hr. The reaction mixture was added to a 5 g SCX cartridge and washed with methanol, the product was eluted with 10% methanolic ammonia. The product was triturated with water to give a beige solid (39.7 mg); δH [$^2H_6$] DMSO 9.32 (1H, s), 9.22 (1H, s), 8.64 (2H, m), 8.19 (1H, s), 7.87 (1H, d), 7.56 (4H, m), 7.27 (6H, m), 7.02 (1H, d), 4.07 (2H, s), 3.42 (2H, t), 3.14 (5H, m);m/z 531.

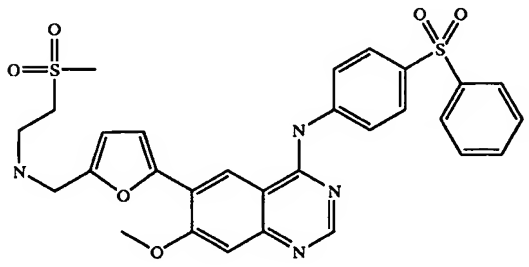
Example 32



(4-Phenoxyphenyl)-(7-(5-(2-(methanesulphonyl) ethylaminomethyl)furan-2-yl)-quinolin-4-yl)amine

5-(4-(4-phenoxyphenylamino)-quinolin-7-yl)furan-2-carbaldehyde (0.05 g) was reacted with 2-(methanesulphonyl)ethylamine (0.075 g) according to procedure D. Acidification with acetic acid (0.5 ml) followed by purification using a ion-exchange (SCX) Bond Elut™ cartridge, eluting with methanol-ammonia (9:1), concentration and trituration with diethylether afforded an off-white solid; δH [$^2H_6$]DMSO 8.44 (1H, d), 8.41 (1H, d), 8.11 (1H, s), 7.85 (1H, d), 7.44–7.35 (4H, m), 7.18–7.03 (6H, m), 6.79 (1H, d), 6.47 (1H, d), 3.82 (2H, s), 3.01 (2H, t); m/z 514 $(M+1)^+$.

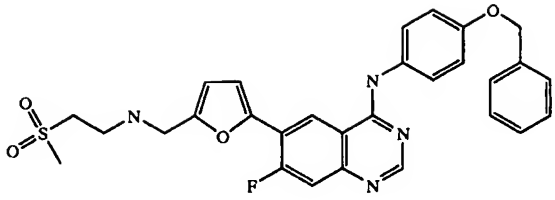
Example 33



6-[5-({[2-(Methanesulphonyl)ethyl]amino}methyl)-2-furyl]-7-methoxy-N-(4benzenesulphonyl)phenyl-4-quinazolinamine

Prepared according to Procedure D from 5-(7-methoxy-4-(4-benzenesulphonyl)phenylamino-quinazolin-6-yl) furan-2-carbaldehyde hydrochloride (0.6 equiv) and 2-methanesulphonyl (1 equiv). δ^1H NMR (400 MHz, DMSO-d_6) 10.23 (s, 1H), 8.76(s, 1H), 8.59 (s, 1H), 8.14 (d, 2H), 7.96 (m, 4H), 7.59–7.71 (m, 3H), 7.33 (s, 1H), 7.03 (d, 1H), 6.47 (d, 1H), 4.06 (s, 3H), 3.86 (s, 2H), 3.27 (t, 2H), 3.00 (s, 3H), 2.98 (t, 2H). ESI-MS m/z 593(M+1).

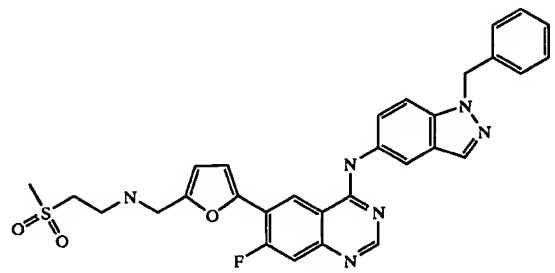
Example 34



N-[4-(Benzyloxy)phenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from a mixture of 5-(4-(4-benzyloxy-phenylamino)-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde hydrochloride (0.13 grams) in 1,2-dichloroethane (3 ml), diisopropylethylamine (65 mg), acetic acid (45 mg), 2-methanesulphonylethylamine (0.125 grams), and sodium triacetoxyborohydride (0.27 grams). The mixture was stirred for 18 hours. The reaction mixture was quenched with methanol (3 ml) and poured into a separatory funnel containing aqueous saturated sodium hydrogen carbonate (100 ml) and ethyl acetate (100 ml). The mixture was extracted. The organic layer was washed with water. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was treated with ethyl acetate/hexanes and collected by filtration (0.083 g, 61% yield). δ^1H NMR (400 MHz, DMSO-d_6) 9.98(s, 1H), 8.83(d, 1H), 8.44(s, 1H), 7.58(m, 3H), 7.44(m, 2H), 7.37(m, 2H), 7.31(m, 1H), 7.03(d, 1H), 6.91(m, 1H), 6.5(d, 1H), 5.1(s, 2H), 3.84(s, 1H), 3.25(m, 2H), 2.99(s, 3H), 2.96(m, 2H). ESI-MS m/z 545(M−1).

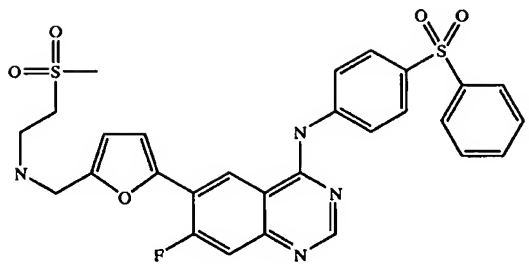
Example 35



N-(1-Benzyl-1H-indazol-5-yl)-7-fluoro-[5-({[2 (methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-(1-Benzyl-1H-indazol-5-ylamino)-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). δ^1H NMR (400 MHz, DMSO-d_6) 10.16(s, 1H), 8.91 (d, 1H), 8.46(s, 1H), 8.11(s, 2H), 7.65(m, 3H), 7.26(m, 5H), 6.93(m, 1H), 6.54(d, 2H), 5.65(s, 2H), 3.89(s, 2H), 3.28(m, 2H), 2.99(m, 5H). ESI-MS m/z 569 (M−1).

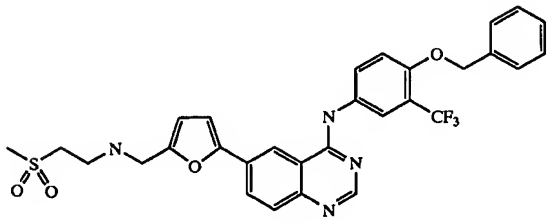
Example 36



N-[4-(Phenylsulphonyl)phenyl]-7-fluoro-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Prepared according to Procedure D from 5-(4-(4-Phenyzsulphonylphenylamino)-7-fluoro-quinazolin-6-yl)-furan-2-carbaldehyde (0.6 equiv) and 2-methanesulphonyl-ethylamine (1 equiv). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.38(s, 1H), 8.87(d, 1H), 8.62(s, 1H), 8.11 (d, 2H), 7.95(m, 4H), 7.63(m, 4H), 6.94(m, 1H), 6.51(d, 1H), 3.84(s, 2H), 3.25(m, 2H), 2.98(s, 3H), 2.95(m, 2H). ESI-MS m/z 579 (M−1).

Example 37



N-(3-Trifluoromethyl-4-benzyloxyphenyl)-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-4-furyl]-4-quinazolinamine

The mixture of 5-(4-(4-benzyloxy-3-trifluoromethylphenylamino)-quinazolin-6-yl)-furan-2-carbaldehyde (211 mg, 0.40 mmol), 2-methanesulphonyl-ethylamine (99 mg, 2.0 mmol), acetic acid (0.5 ml) in dichloromethane (15 ml) was stirred at room temperature for 1.5 hours then was heated to reflux for 1 hour. The mixture was cooled to 0° C. with ice bath. Sodium cyanoborohydride (50 mg, 0.8 mmol) was added at 0° C. The reaction mixture then was stirred at room temperature for 1 hour. Diluted with ethyl acetate (50 ml), then quenched with saturated sodium bicarbonate solution slowly. Extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the resulting residue was accomplished using flash chromatography on silica gel with 2% methanol in ethyl acetate which afforded a yellow solid (0.10 g, 43% yield). H^1 NMR (400 MHz, DMSO). δ10.0 (s, 1H), 8.7 (s, 1H), 8.5 (s, 1H), 8.1 (d, 1H), 8.1 (s, 2H), 7.8 (d, 1H), 7.4 (m, 5H), 7.3 (m, 1H), 7.0 (d, 1H), 6.5 (d, 1H), 5.3 (s, 2H), 3.8 (s, 2H), 3.2 (m, 2H), 3.0 (s, 3H), 2.9 (m, 2H). ESI-MS m/z 597 $(M+H)^+$.

Further Examples

The compounds in Lists 1 to 48 above and their hydrochloride salts, if appropriate, are prepared by analogous techniques using the appropriate starting materials.

Biological Data

Compounds of the present invention were tested for protein tyrosine kinase inhibitory activity in substrate phosphorylation assays and cell proliferation assays.

Substrate Phosphorylation Assay

The substrate phosphorylation assays use baculovirus expressed, recombinant constructs of the intracellular domains of c-erbB-2 and c-erbB-4 that are constitutively active and EGFr isolated from solubilised A431 cell membranes. The method measures the ability of the isolated enzymes to catalyse the transfer of the g-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide (Biotin-GluGluGluGluTyrPheGluLeuVal). Substrate phosphorylation was detected following either of the following two procedures: a.) c-ErbB-2, c-ErbB4 or EGFr were incubated for 30 minutes, at room temperature, with 10 mM $MnCl_2$, 10 mM ATP, 5 mM peptide, and test compound (diluted from a 5 mM stock in DMSO, final DMSO concentration is 2%) in 40 mM HEPES buffer, pH 7.4. The reaction was stopped by the addition of EDTA (final concentration 0.15 mM) and a sample was transferred to a streptavidin-coated 96-well plate. The plate was washed and the level of phosphotyrosine on the peptide was determined using a Europium-labelled antiphosphotyrosine antibody and quantified with a time-resolved fluorescence technique. b.) ErbB2 was incubated for 50 minutes at room temperature with 15 mM $MnCl_{2,2}$ mM ATP, 0.25 mCi [γ-^{33}P] ATP/well, 5 mM peptide substrate, and test compound (diluted from a 10 mM stock in DMSO, final DMSO concentration is 2%) in 50 mM MOPS pH 7.2. The reaction was terminated by the addition of 200 ml of PBS containing 2.5 mg/ml streptavidin-coated SPA beads (Amersham Inc.), 50 mM ATP, 10 mM EDTA and 0.1%TX-100. The microtitre plates were sealed and SPA beads were allowed to settle for at least six hours. The SPA signal was measured using a Packard Topcount 96-well plate scintillation counter (Packard Instrument Co., Meriden, Conn.).

The results are shown in Tables 1 A (examples 1 to 7) and 1 B (examples 8 to 29 and 33 to 37) as the IC_{50} values.

TABLE 1A

	Substrate Phosphorylation	
Example	erbB2 - assay (b)	EGF-r - assay (a)
1	+++	+++
2	+++	+++
3	+++	+++
4	++	+++
5	+++	+++
6	++	
7	+++	+++

TABLE 1B

Example	Substrate Phosphorylation erbB2 - assay (b)
8	+++
9	+++
10	+++
11	+++
12	++
13	++
14	+++

TABLE 1B-continued

15	+++
16	+++
17	+++
18	+++
19	+++
20	+++
21	+++
22	+++
23	+++
24	+++
25	+++
26	+++
27	+++
28	+++
29	+++
33	+++
34	+++
35	+++
36	+++
37	+++

IC_{50} values	Symbol
<0.10 μM	+++
0.10–1.0 μM	++
1.0–10.0 μM	+
>10.0 μM	-
Not determined	ND

Cellular Assays: Methylene Blue Growth Inhibition Assay

Human breast (BT474), head and neck (HN5) and gastric tumor (N87) cell lines were cultured in low glucose DMEM (Life Technologies 12320-032) containing 10% fetal bovine serum (FBS) at 37° C. in a humidified 10% CO_2, 90% air incubator. The SV40 transformed human mammary epithelial cell line HB4a was transfected with either human H-ras cDNA (HB4a r4.2) or the human c-erbB2 cDNA (HB4a c5.2). The HB4a clones were cultured in RPMI containing 10% FBS, insulin (5 μg/ml), hydrocortisone (5 μg/ml), supplemented with the selection agent hygromycin B (50 μg/ml). Cells were harvested using trypsin/EDTA, counted using a haemocytometer, and plated in 100 ml of the appropriate media, at the following densities, in a 96-well tissue culture plate (Falcon 3075): BT474 10,000 cells/well, HN5 3,000 cells/well, N87 10,000 cells/well, HB4a c5.2 3,000 cells/well, HB4a r4.2 3,000 cells/well. The next day, compounds were diluted in DMEM containing 100 mg/ml gentamicin, at twice the final required concentration, from 10 mM stock solutions in DMSO. 100 ml/well of these dilutions were added to the 100 ml of media currently on the cell plates. Medium containing 0.6% DMSO was added to control wells. Compounds diluted in DMEM were added to all cell lines, including the HB4a r4.2 and HB4a c5.2 cell lines. The final concentration of DMSO in all wells was 0.3%. Cells were incubated at 37° C., 10% CO_2 for 3 days. Medium was removed by aspiration. Cell biomass was estimated by staining cells with 100 per well methylene blue (Sigma M9140, 0.5% in 50:50 ethanol:water), and incubation at room temperature for at least 30 minutes. Stain was removed, and the plates rinsed under a gentle stream of water, and air-dried. To release stain from the cells 100 μl of solubilization solution was added (1% N-lauroyl sarcosine, Sodium salt, Sigma L5125, in PBS), and plates were shaken gently for about 30 minutes. Optical density at 620 nM was measured on a microplate reader. Percent inhibition of cell growth was calculated relative to vehicle treated control wells. Concentration of compound that inhibits 50% of cell growth (IC_{50}) was interpolated using nonlinear regression (Levenberg-Marquardt) and the equation, $y=V_{max}*(1-(x/(K+x)))+Y2$, where "K" was equal to the IC_{50}.

Table 2 illustrates the inhibitory activity of compounds of the present invention as IC_{50} values in, μM against a range of tumor cell lines.

TABLE 2

	Cell Proliferation				
Example	HB4a erbB2	HB4a ras	BT474	HN5	N87
1	+++	+	+++	+++	+++
2	+++	+	+++	+++	+++
3	+++	+	+++	+++	+++
4	+++	-	+++	+++	+++
5	+++	-	+++	+++	+++
6	+++	+	+++	+++	+++
7	+++	++	+++	+++	+++
8	+++	++	+++	+++	+++
9	+++	++	+++	+++	+++
10	+++	++	+++	+++	+++
11	+++	-	+++	+++	+++
12	+++	-	+++	++	+++
13	++	-	++	+	++
14	+++	-	+++	+++	+++
15	+++	-	+++	+++	+++
16	+++	++	+++	+++	+++
17	++	++	+++	++	++
18	+++	++	+++	+++	+++
19	+++	-	+++	+++	+++
20	+++	-	+++	++	+++
21	+++	++	+++	+++	+++
22	+++	+	+++	+++	+++
23	+++	+	+++	+++	+++
24	++	-	++	+++	++
25	+++	-	+++	+++	+++
26	+++	++	+++	+++	+++
27	+++	++	+++	+++	+++
28	+++	+	+++	+++	+++
29	+++	-	+++	+++	+++
33	+++	+++	+++	+++	+++
34	+++	-	+++	+++	+++
35	+++	+	+++	+++	+++
36	++	-	++	++	++
37	+++	+	+++	+++	+++

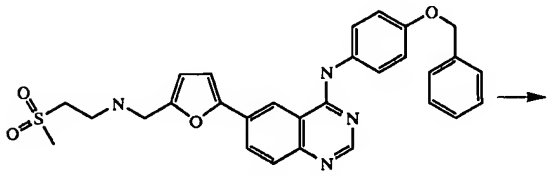
IC_{50} values	Symbol
<5 μM	+++
5–25 μM	++
25–50 μM	+
>50 μM	-
Not determined	ND

Major Metabolites

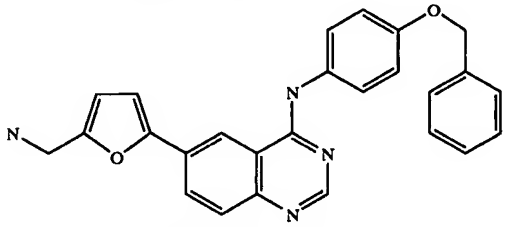
Liver S-9 homogenates (5 mg/mL protein concentration) from prepared pooled male Sprague Dawley rat livers and pooled human livers (XenoTech, LLC, Kansas City, Kans.) were incubated in 96-well polypropylene plates with representative examples selected from examples 1 to 40 (10 μM) in a total volume of 0.5 mL. Stock solutions of these compounds were prepared in DMSO at a concentration of 1 mM to maintain a <1% final DMSO concentration for each reaction. Enzymatic incubations contained cofactors (5.71 mM NADPH, 7.14 mM glucose-6-phosphate, 7.14 mM UDPGA, 47.1 mM potassium chloride, and 11.4 mM magnesium chloride in 0.1 M potassium phosphate buffer, pH 7.4). Control samples were aspirated from the reaction samples at time zero and placed immediately into 2 volumes of ice-chilled acetonitrile. Sample reaction plates were incubated for 60 min in a shaker incubator maintained at 37° C. supplied with O_2. Reactions were terminated by addition of

2 volumes of ice-chilled acetonitrile. All samples were vortexed and centrifuged at 2000×g for 10 min. The supernatant was removed and analyzed by LC-MS. The metabolite identification work was done by using reversed-phase HPLC coupled with ion-trap mass spectroscopy.

For example:

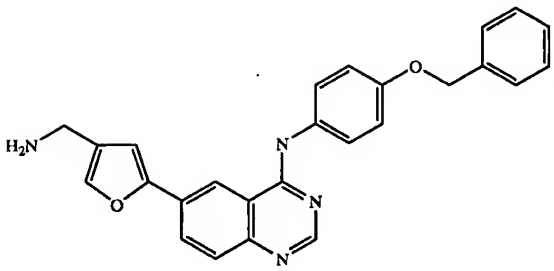


Example 5, m/z 529



N-dealkylated, m/z 423

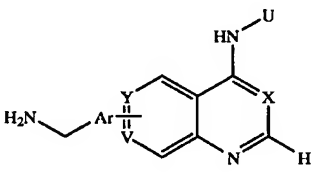
N-[4-(Benzyloxy)phenyl]-6-[4-(aminomethyl)-2-furyl]-4-quinazolinamine



Prepared according to Procedure D and identified as a major metabolite of N-[4-(benzyloxy)phenyl]-6-[4-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine in ^{1}HNMR 300 MHz, $CDCl_3$ 8.69(s, 1H), 8.11 (s, 1H), 8.02 (d, 1H), 7.88 (d, 1H), 7.61 (d, 2H), 7.5–7.2 (m, 7H), 7.05 (d, 2H), 6.83 (s, 1H), 5.10 (s, 2H), 3.82 (s, 2H); MS m/z 423 (M+1).

Thus, particular compounds of interest as metabolites (either as isolated compounds or compounds in vivo) are compounds of formula (XVII):

(XVII)



in which Ar, Y, V, X and U are as defined above; all possible preferments for these groups as defined above are applicable.

Compounds of formula (XII) of special interest include:

4-(4-Fluorobenzyloxy)-phenyl)-(6-(5-(aminomethyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-(3-Fluorobenzyloxy)-phenyl)-(6-(5-(aminomethyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzenesulphonyl-phenyl)-(6-(5-(aminomethyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(3-(aminomethyl)phenyl-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(5-(aminomethyl)-furan-2-yl)-quinazolin-4-yl)-amine;

(4-(3-Fluorobenzyloxy-phenyl)-(6-(4-(aminomethyl)-furan-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(4-Benzyloxy-phenyl)-(6-(2-(aminomethyl)-thiazol-4-yl)-quinazolin-4-yl)-amine;

N-{4-[(3-Fluorobenzyl)oxy]phenyl}-6-[5-(aminomethyl)-2-furyl]-4-quinazolinamine;

N-{4-[(3-Fluorobenzyl)oxy]-3-methoxyphenyl}-6-[5-(aminomethyl)-2-furyl]-4-quinazolinamine;

N-[4-(Benzyloxy)phenyl]-7-methoxy-6-[5-(aminomethyl)-2-furyl]-4-quinazolinamine;

N-[4-(Benzyloxy)phenyl]-6-[4-(aminomethyl)-2-furyl]-4-quinazolinamine;

N-{4-[(3-Fluorobenzyl)oxy]-3-methoxyphenyl}-6-[2-(aminomethyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-{4-[(3-Bromobenzyl)oxy]phenyl}-6-[2-(aminomethyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-{4-[(3-Fluorobenzyl)oxy]phenyl}-6-[2-(aminomethyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-[4-(Benzyloxy)-3-fluorophenyl]-6-[2-(aminomethyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-(1-Benzyl-1H-indazol-5-yl)-7-methoxy-6-[5-(aminomethyl)-2-furyl]-4-quinazolinamine;

6-[5-(aminomethyl)-2-furyl]-N-(4-{[3-(trifluoromethyl)benzyl]oxy}phenyl)-4-quinazolinamine;

N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-(aminomethyl)-2-furyl]-4-quinazolinamine;

N-{4-[(3-Bromobenzyl)oxy]phenyl}-6-[5-(aminomethyl)-2-furyl]-4-quinazolinamine;

N-[4-(Benzyloxy)phenyl]—6-[-(aminomethyl)-2-furyl]-4-quinazolinamine;

N-[1-(3-Fluorobenzyl)-1H-indazol-5-yl]-6-[2-(aminomethyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

6-[5-(Aminomethyl)-2-furyl]-N-[4-(benzenesulphonyl)phenyl]-4-quinazolinamine;

6-[2-(Aminomethyl)-1,3-thiazol-4-yl]-N-[4-(benzenesulphonyl)phenyl]-4-quinazolinamine;

6-[2-(Aminomethyl)-1,3-thiazol-4-yl]-N-(4-{[3-(trifluoromethyl)benzyl]oxy}phenyl)-4-quinazolinamine

N-{3-Fluoro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[2-(aminomethyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-(1-Benzyl-1H-indazol-5-yl)-6-[2-(aminomethyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-(3-Fluoro-4-benzyloxyphenyl)-6-[2-(aminomethyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-(3-Chloro-4-benzyloxyphenyl)-6-[2-(aminomethyl)-1,3-thiazol-4-yl]-4-quinazolinamine;

N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-(aminomethyl)-2-furyl]-4-quinazolinamine;

(4-Phenoxyphenyl)-(7-(2-(aminomethyl)-thiazol-4-yl)-quinolin-4-yl)amine;

(4-Phenoxyphenyl)-(7-(4-(aminomethyl)-thiazol-5-yl)-quinolin-4-yl)amine;

(4-Phenoxyphenyl)-(7-(5-(aminomethyl)-furan-2-yl)-quinolin-4-yl)amine;

6-[5-(Aminomethyl)-2-furyl]-7-methoxy-N-(4-phenylsulphonyl)phenyl-4-quinazolinamine;

N-[4-(Benzyloxy)phenyl]-7-fluoro-6-[5-(aminomethyl)-2-furyl]-4-quinazolinamine;

N-(1-Benzyl-1H-indazol-5-yl)-7-fluoro-6-[5-(aminomethyl)-2-furyl]-4-quinazolinamine;

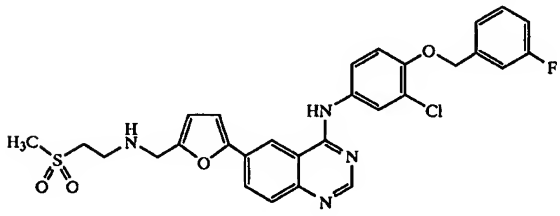
N-[4-(Benzenesulphonyl)phenyl]-7-fluoro-6-[5-(aminomethyl)-2-furyl]-4-quinazolinamine;

N-(3-Trifluoromethyl-4-benzyloxyphenyl)-6-[5-(aminomethyl)-4-furyl]-4-quinazolinamine;

and salts or solvates thereof, particularly pharmaceutically acceptable salts thereof.

We claim:

1. A compound of the formula:



and salts or solvates thereof.

2. A pharmaceutical formulation, comprising: the compound of claim 1 or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers, diluents, or excipients.

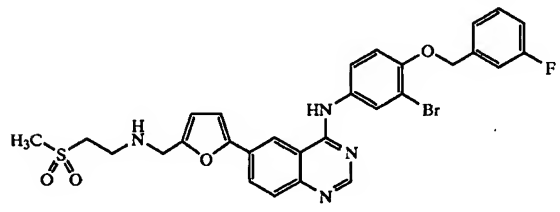
3. A method of treating a susceptible cancer in a human or animal subject mammal, comprising administering to said subject an effective amount of a compound as claimed in claim 1, wherein said cancer is breast cancer, gastric cancer or head and neck cancer.

4. A method as claimed in claim 3, wherein the susceptible cancer is breast cancer.

5. A method as claimed in claim 3, wherein the susceptible cancer is gastric cancer.

6. A method as claimed in claim 3, wherein the susceptible cancer is head and neck cancer.

7. A compound of the formula:



and salts or solvates thereof.

8. A pharmaceutical formulation, comprising: the compound of claim 7 or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers, diluents, or excipients.

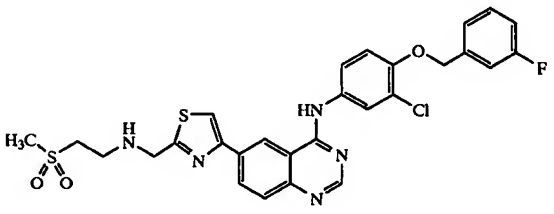
9. A method of treating a susceptible cancer in a human or animal subject mammal, comprising administering to said subject an effective amount of a compound as claimed in claim 7, wherein said cancer is breast cancer, gastric cancer or head and neck cancer.

10. A method as claimed in claim 9, wherein the susceptible cancer is breast cancer.

11. A method as claimed in claim 9, wherein the susceptible cancer is gastric cancer.

12. A method as claimed in claim 9, wherein the susceptible cancer is head and neck cancer.

13. A compound of the formula:



and salts or solvates thereof.

14. A pharmaceutical formulation, comprising: the compound of claim 13 or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers, diluents, or excipients.

15. A method of treating a susceptible cancer in a human or animal subject mammal, comprising administering to said subject an effective amount of a compound as claimed in claim 13, wherein said cancer is breast cancer, gastric cancer or head and neck cancer.

16. A method as claimed in claim 15, wherein the susceptible cancer is breast cancer.

17. A method as claimed in claim 15, wherein the susceptible cancer is gastric cancer.

18. A method as claimed in claim 15, wherein the susceptible cancer is head and neck cancer.

* * * * *

EXHIBIT 8A

Certificate of Correction

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,485 B2
DATED : March 30, 2004
INVENTOR(S) : Malcolm Carter et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [*] Notice, insert the following:
-- The portion of the term of this patent subsequent to January 8, 2019 has been disclaimed --.

Column 1,
Line 22, replace "Ick" with -- lck --.
Line 46, replace "eg" with -- e.g. --.

Column 2,
Lines 6, 9, 35 and 37, replace "Ick" with -- lck --.

Column 4,
Lines 25 and 31, replace "Ick" with -- lck"

Column 10,
Line 48, replace "fu ran-2-yl)" with -- furan-2-yl) --.

Column 18,
Line 33, replace "thiazol-2-y)" with -- thiazol-2-yl) --.

Column 23,
Line 36, replace "[5-(I[2-(methanesulphonyl)" with -- [5-({[2-(methanesulphonyl) --.

Column 33,
Lines 44 and 54, replace "Ick" with -- lck --.

Column 36,
Lines 29 and 64, replace "tic" with -- tlc --.

Column 37,
Line 29, replace "tic" with -- tlc --.

Column 38,
Line 59, replace "(α-bromoketone" with -- α-bromoketone --.

Column 50,
Lines 32 and 33, immediately after "5.20 (s, 2H); MS m/z 490 (M+1)" and immediately before "6-Iodo-(4-(3-fluorobenzyloxy)-3-methoxyphenyl)-quinazolin-4yl)amine", insert a space.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,485 B2
DATED : March 30, 2004
INVENTOR(S) : Malcolm Carter et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 53,
Line 31, replace "2-to (tributylstannyl)" with -- 2-(tributylstannyl) --.

Column 54,
Between lines 62 and 63, insert a space.

Column 59,
Line 61, replace "(4-(3-Fluorobenzyl oxy)" with -- (4-(3-Fluorobenzyloxy) --.

Column 67,
Line 37, replace "N-{4-[(3-bromobenzyl)oxy]phenyl}-6-[5-(J[2-" with
-- N-{4-[(3-bromobenzyl)oxy]phenyl}-6-[5-({[2- --.

Column 75,
Line 20, replace "Phenyzsulphonylphenylamino)" with
-- Phenylsulphonylphenylamino) --.

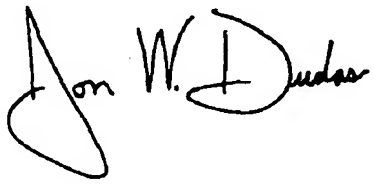
Column 76,
Line 13, replace "g-phosphate" with -- γ-phosphate --.

Column 81,
Lines 24 and 40, replace "and salts or solvates" with -- or salts or solvates --.

Column 82,
Line 19, replace "and salts or solvates" with -- or salts or solvates --.

Signed and Sealed this

Sixth Day of September, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT 8B

Terminal Disclaimer

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING SECOND APPLICATION

Docket No.
PG3416US2

In re Application of: **Carter et al.**
Application No. **10/071,358**
Filed: **February 8, 2002**
For: **HETEROCYCLIC COMPOUNDS**

The owner, **SmithKline Beecham Corporation** of **100.00** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173 as shortened by any terminal disclaimer filed prior to the grant of any patent g granted on pending second Application Number **09/582,746**, filed on **June 30, 2000**. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the second application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of any patent granted on the second application, as shortened by any terminal disclaimer filed prior to the patent grant, in the event that any such granted patent: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

3. Owner/applicant is ☐ Small entity ☒ Large entity

The terminal disclaimer fee under 37 CFR 1.20(d) is **$110.00** and is to be paid as follows:

☐ A check in the amount of the fee is enclosed.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number **07-1392**.

PTO suggested wording for terminal disclaimer was

☒ unchanged. ☐ changed (if changed, an explanation should be supplied.)

Signature

Dated: 8/26/03

Name and Address of Person Signing

John L. Lemanowicz, Reg. No. 37,380
Attorney for Applicants
GlaxoSmithKline
Five Moore Drive, PO Box 13398
Research Triangle Park, NC 27709-3398
Telephone: (919) 483-8247
Facsimile: (919) 483-7988

I certify that this document and fee is being deposited on with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Signature of Person Mailing Correspondence

Typed or Printed Name of Person Mailing Correspondence

EXHIBIT 8C

Request for Second Certificate of Correction

PATENT
2801-0209X

IN THE U.S. PATENT AND TRADEMARK OFFICE

Patentee: Malcolm Carter et al.

Patent No.: 6,713,485 B2

Filed: February 8, 2002

Issue Date: March 30, 2004

For: HETEROCYCLIC COMPOUNDS

ATTN: CERTIFICATE OF CORRECTIONS BRANCH

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 C.F.R. § 1.322

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

October 7, 2005

Sir:

Attached hereto is a Certificate of Correction (Form PTO-1050) in connection with the above-identified patent.

It is noted that the attached Certificate of Correction form is being filed to correct the inventorship of the claimed invention. Specifically, KATHRYN JANE SMITH has been deleted as an inventor of the claimed subject matter. Upon further review of the patented claims, the patentee realized that KATHRYN JANE SMITH should have been deleted as an inventor upon amendment of the claims during examination. This error occurred without deceptive intent.

The fee under 37 C.F.R. § 1.20(a) of $100.00 is attached hereto. Also attached hereto, in compliance with the requirements of 37 C.F.R.§1.1.324 and M.P.E.P. §1481 are the

following:

(1) Petition under 37 C.F.R.§1.1.324(a)

(2) Statements from the current named inventors

(3) Statement from the assignee; and

(4) The fee set forth in 37 C.F.R.§1.20(b)

Please charge any fees or credit any overpayment pursuant to 37 C.F.R. § 1.20 to Deposit Account No. 02-2448.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
MaryAnne Armstrong, #40,069

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

2801-0209X

Attachment(s): Certificate of Correction (Form PTO-1050)
Fee under 37 C.F.R. §1.20(a)
Petition under 37 C.F.R.§1.1.324(a)
Statements from the current named inventors
Statement from the assignee; and
The fee set forth in 37 C.F.R.§1.20(b)

PTO/SB/44 (08-00)
Approved for use through 6/30/99. OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,485 B2

DATED : March 30, 2004

INVENTOR(S): Malcolm Carter et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Page 1, left column, in field (75) "Inventors", please delete **KATHRYN JANE SMITH** as an inventor.

MAILING ADDRESS OF SENDER:
2801-0209X -MAA
BIRCH, STEWART, KOLASCH & BIRCH, LLP
PTO BOX 16X

PATENT NO. 6,713,485 B2

No. of Additional copies
— 0

2801-0209X
PATENT

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: Malcolm CARTER et al.

Patent No.: 6,713,485 B2

Filed: February 8, 2002

Issued: March 30, 2004

For: HETEROCYCLIC COMPOUNDS

PETITION UNDER 37 C.F.R.§1.324 TO CORRECT THE INVENTORSHIP OF A PATENT

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

October 7, 2005

Sir:

The undersigned respectfully petition under 37 C.F.R.§1.324 on behalf of the Patentee that the Director issue the attached Certificate of Correction to correct the inventorship of US Patent No. 6,713,485 B2. Specifically, the inventorship of the patent is to be corrected by deletion of KATHRYN JANE SMITH as a named inventor of the claimed subject matter.

In fulfillment of the requirements under 37 C.F.R.§1.324, attached hereto are the following:

(1) A statement from the current named inventors, who are listed below, stating that they have no disagreement with the requested change.

Currently Name Inventors:

i) Malcolm Clive Carter

ii) George Stuart Cockerill

iii) Stephen Barry Guntrip

iv) Karen Elizabeth Lackey

v) Kathryn Jane Smith

(2) A statement from the assignee of the patent, SmithKline Beecham Corporation, which complies with the requirements under 37 C.F.R.§3.73(b) and which agrees to the requested change of inventorship.

(3) The fee of $130.00 as set forth under 37 C.F.R.§1.20(b).

If there are any questions regarding the present petition or the Examiner requires any additional information, please contact MaryAnne Armstrong, PhD (Reg. No. 40,069) at (703) 205-8063.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
MaryAnne Armstrong, #40,069

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/MAA

Attachments:
- ☒ Fee Payment
- ☒ Statement of all current inventors
- ☒ Statement of Assignee
- ☒ Certificate of Correction

STATEMENT FROM THE ASSIGNEE UNDER 37 C.F.R.§§1.324 and 3.73(b) FOR A PETITION TO CORRECT THE INVENTORSHIP OF A PATENT

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Under the requirements of 37 C.F.R. §§ 1.324 and 3.73(b), the Assignee of US Pat. Nos. 6,713,485 B2 and 6,727,256, SmithKline Beecham Corporation, agrees to the requested change of inventorship, whereby KATHRYN JANE SMITH will be deleted as a named inventor of the claimed subject matter. In compliance with the requirements of 37 C.F.R.§3.73(b)(1)-(2) attached hereto are the following:

(1) *Documentary evidence of the chain of title from the inventors to the assignee.* In this regard, attached hereto is a copy of the recorded assignment, which transferred ownership from the inventors to Glaxo Wellcome, Inc.. Also attached is a copy of the merger documents recorded with the USPTO on May 2, 2005, which shows the merger of Glaxo Wellcome, Inc. into SmithKline Beecham Corporation, the named Assignee listed on the front of US Pat. Nos. 6,713,485 B2 and 6,727,256.

(2) *A showing that the undersigned,* Charles E. Dadswell, *is authorized to act on behalf of the assignee.* I, Charles E. Dadswell, am authorized to act on behalf of the Assignee, SmithKline Beecham Corporation.

By _____ Date 07/21/2005

Charles E. Dadswell, Attorney

(Resolution Attached)

Attachments: Assignment and merger documents

Power of Attorney

BY THIS POWER OF ATTORNEY given this 23rd day of February two thousand and five **SMITHKLINE BEECHAM CORPORATION,** a company incorporated in Pennsylvania (Registration No. 3330395) and having its registered office at One Franklin Plaza, P.O. Box 7929, Philadelphia, Pennsylvania 19101, United States of America, (hereinafter called "the Company"), **HEREBY** appoints all and any of its Directors, Secretary and Assistant Secretary for the time being, and **DAVID ROBERTS, PETER JOHN GIDDINGS, ARTHUR WILLIAM RUSSELL TYRRELL, HUGH BAINFORDE DAWSON, WENDY ANNE FILLER, MICHAEL JOHN STOTT, PETER I. DOLTON, HELEN KAYE QUILLIN, MARCUS JONATHAN WILLIAM DALTON, CHARLES M. KINZIG, STEPHEN VENETIANER, THEODORE R. FURMAN, MARY E. McCARTHY, EDWARD R. GIMMI, CHARLES EDWARD DADSWELL, ROBERT H. BRINK, and FRANK P. GRASSLER** jointly and severally to be its true and lawful agents and attorneys (hereinafter called "the Attorneys") on behalf and in the name of the Company or otherwise to do, perform, exercise or execute or concur with any other person or persons in doing, performing or exercising in or for any country or countries or jurisdiction in any part of the world all or any of the following powers, acts, deeds and things in connection with: letters patent, including extensions thereto; utility models; copyrights; trademark registrations; trademarks; trade names; trade dress; logos; design rights; designs and all rights analogous thereto and all applications therefor and any other forms whatsoever of intellectual property rights; including know-how, all of which are hereinafter called "Intellectual Property Rights", that is to say:

1. In any country or countries or jurisdiction in any part of the world to make application or cause application to be made for the grant or issue or transfer to the Company or registration in its name of Intellectual Property Rights and to take all steps necessary for the same to be prosecuted, maintained, withdrawn, renewed, enforced, defended or extended.

2. As the act and deed of the Company to sign, seal, deliver and execute all or any assignments or assurances, licences to the Company of or under any Intellectual Property Rights or the right to and interest in any inventions to be the subject of Intellectual Property Rights for the purpose of fully and effectually vesting and transferring the same in and to the Company.

3. As the act and deed of the Company to sign and execute all or any assignments and acceptances of the transfer or assignment of such rights, and also any licences, sub-licences and consents from the Company of or under any Intellectual Property Rights or the right to and interest in any invention to be the subject of Intellectual Property Rights, for the purpose of fully and effectually vesting transferring or granting the same in and to any entity, whether in the United Kingdom or elsewhere, in so far as such documents can be executed without the Company's seal being affixed thereto. For purposes of this Power of Attorney, the terms "entity" means, and includes, any person, firm or company or group of persons or unincorporated body.

4. To give undertakings or assurances to third parties and to any Trademark Registry or official intellectual property agency or governmental department or otherwise responsible for the registration or protection of trademarks, trade names, trade dress, logos, design rights or designs for the purpose of best protecting or ensuring the co-existence of the Company's rights to trademarks, trade names, trade dress, logos, design rights or designs.

5. To commence, prosecute and defend any proceedings or applications whether judicial or extra judicial relating to Intellectual Property Rights and to maintain, withdraw or settle the same.

6. For and in connection with any Intellectual Property Rights to sign, seal, deliver and execute any Power of Attorney or other deed or document authorising any agent, including trademark and patent agents and attorneys, to act on behalf of the Company.

7. To apply for the registration, amendment or cancellation of user rights in respect of any trademark or trade name.

8. To act in regard to all official communications which may now or hereafter be addressed to the Attorneys relating to Intellectual Property Rights or the renewal thereof in such manner that the Attorneys may be recognised as the authorised agent(s) of the Company in all proceedings in relation thereto.

9. For all or any of the purposes contained herein as the act and deed of the Company to sign, seal, deliver, execute and do all such documents, deeds, agreements, instruments and to do such acts as shall be requisite or may be deemed proper for or in relation to the said purposes.

10. This Power of Attorney shall expire on December 31, 2006

AND THE COMPANY HEREBY RATIFIES and confirms and agrees to ratify and confirm all and whatsoever the Attorneys or any person, persons, firm or company appointed by them shall lawfully do or have done by virtue of the authorities herein contained

AND THE COMPANY HEREBY DECLARES that all instruments executed under and by virtue of this Power shall be as valid and effectual as if sealed by the Common Seal of the Company.

IN WITNESS whereof **SMITHKLINE BEECHAM CORPORATION** has caused its Common Seal to be hereunto affixed the day and year first before written

The **COMMON SEAL** of)
SMITHKLINE BEECHAM CORPORATION)
was hereto affixed in the presence of:)

Donald F. Parman

Donald F. Parman
Vice President and Secretary

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 2

Patent #: 6727256 **Issue Dt:** 04/27/2004 **Application #:** 09582746 **Filing Dt:** 06/30/2000

PCT #: EP9900048

Inventors: MALCOLM CLIVE CARTER, GEORGE STUART COCKERILL, STEPHEN BARRY GUNTRIP et al

Title: BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS

Assignment: 1

Reel/Frame: 009804/0668 **Recorded:** 03/01/1999 **Pages:** 6

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: KAREN ELIZABETH LACKEY **Exec Dt:** 01/08/1999

Assignees: GLAXO WELLCOME INC.
P.O. BOX 13398 GLOBAL INTELLECTUAL PROPERTY DEPT.
FIVE MOORE DRIVE
RTP, NORTH CAROLINA 27709
GLAXO GROUP LIMITED
GLOBAL INTELLECTUAL PROPERTY DEPT.
BERKELEY AVENUE
GREENFORD, MIDDLESEX UB6 0NN, UNITED KINGDOM

Correspondent: GLAXO WELLCOME INC., PATENT COUNSEL
DAVID J. LEVY
FIVE MOORE DRIVE
PO BOX 13398
RTP NC 27709

Assignment: 2

Reel/Frame: 011281/0024 **Recorded:** 11/14/2000 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: CATRER, MALCOLM CLIVE **Exec Dt:** 06/15/2000
COCKERILL, GEORGE STUART **Exec Dt:** 06/15/2000
GUNTRIP, STEPHEN BARRY **Exec Dt:** 06/15/2000
SMITH, KATHRYN JANE **Exec Dt:** 06/15/2000

Assignee: GLAXO WELLCOME INC.
GLOBAL INTELLECTUAL PROPERTY DEPARTMENT
FIVE MOORE DRIVE, PO BOX 13398
RESEARCH TRIANGLE PARK, NORTH CAROLINA 27709

Correspondent: GLAXO WELLCOME INC.
DAVID J. LEVY
FIVE MOORE DRIVE

PO BOX 13398
RTP NC 27709

Search Results as of: 09/04/2005 01:24 PM

If you have any comments or questions concerning the data displayed, contact OPR / Assignments at 703-308-9723

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

GLAXO WELLCOME, INC.

Additional name(s) of conveying party(ies) attached? ☐ YES ☒ NO

3. Nature of conveyance:

☐ Assignment ☒ Merger
☐ Security Agreement ☐ Change of Name
☐ Other:

Execution Date: March 31, 2001

2. Name and address of receiving party(ies)

Name: SMITHKLINE BEECHAM CORPORATION

Internal Address:

Street Address: One Franklin Plaza

P.O. Box 7929

City: Philadelphia State: PA ZIP: 19101

Country: Postal Code:

Additional name(s) & address(es) attached? ☐ YES ☒ NO

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No(s).

B. Patent No.(s).

6,713,485 B2

6,727,256 B1

Additional numbers attached? ☐ YES ☒ NO

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: BIRCH, STEWART, KOLASCH & BIRCH, LLP

Street Address: P.O. BOX 747

City: FALLS CHURCH State: VA ZIP: 22040-0747

Country: USA

6. Total No. of applications/patents involved: two (2)

7. Total fee (37 C.F.R. § 3.41): $80.00

☒ Enclosed

☒ Authorized to be charged to deposit account, if no fee attached.

8. Deposit account number: 02-2448

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

MaryAnne Armstrong, #40,069
Name of Person Signing/Reg. No.

maa
Signature

May 2, 2005
Date

Total number of pages including cover sheet, attachments, and document: four (4)

MAA/csm/geb

COMMONWEALTH OF PENNSYLVANIA

DEPARTMENT OF STATE

APRIL 05, 2001

TO ALL WHOM THESE PRESENTS SHALL COME, GREETING:

SMITHKLINE BEECHAM CORPORATION

I, Kim Pizzingrilli, Secretary of the Commonwealth of Pennsylvania do hereby certify that the foregoing and annexed is a true and correct photocopy of Articles of Merger restating the Articles of Incorporation in their entirety

which appear of record in this department

IN TESTIMONY WHEREOF, I have hereunto set my hand and caused the Seal of the Secretary's Office to be affixed, the day and year above written.

Kim Pizzingrilli

Secretary of the Commonwealth

DPOS

200124-955

MAR 3 0 2001

Microfilm Number _____

Filed with the Department of State on _____

Entity Number 533095

_____
Secretary of the Commonwealth

JK

ARTICLES OF MERGER-DOMESTIC BUSINESS CORPORATION

(DSCB:15-1924 (Rev 99))

In compliance with the requirements of 15 Pa.C.S. § 1924 (relating to articles of merger or consolidation), the undersigned business corporations, desiring to effect a merger, hereby state that:

1. The name of the corporation surviving the merger is: SmithKline Beecham Corporation

2. (Check and complete one of the following):

X The surviving corporation is a domestic business corporation and the (a) address of its current registered office in this Commonwealth or (b) name of its commercial registered office provider and the county of venue is (the Department is hereby authorized to correct the following information to conform to the records of the Department):

(a) One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102 Phila.
Number and Street City State Zip County

(b) c/o: _____ _____
Name of Commercial Registered Office Provider County

For a corporation represented by a commercial registered office provider, the county in (b) shall be deemed the county in which the corporation is located for venue and official publication purposes.

___ The surviving corporation is a qualified foreign business corporation incorporated under the laws of _____ and the (a) address of its current registered office in this Commonwealth or (b) name of its commercial registered office provider and the county of venue is (the Department is hereby authorized to correct the following information to conform to the records of the Department):

(a) _____
Number and Street City State Zip County

(b) c/o: _____ _____
Name of Commercial Registered Office Provider County

For a corporation represented by a commercial registered office provider, the county in (b) shall be deemed the county in which the corporation is located for venue and official publication purposes.

___ The surviving corporation is a nonqualified foreign business corporation incorporated under the laws of _____ and the address of its principal office under the laws of such domiciliary jurisdiction is:

_____
Number and Street City State Zip

3. The name and the address of the registered office in this Commonwealth or name of its commercial registered office provider and the county of venue of each other domestic business corporation and qualified foreign business corporation which is a party to the plan of merger are as follows:

Name of Corporation	Address of Registered Office or Name of Commercial Registered Office Provider	County
Glaxo Wellcome Inc.	CT Corporation System	Philadelphia

200124 - 956

DSCB:15-1926 (Rev 90)-2

4. (Check, and if appropriate complete, one of the following):

___The plan of merger shall be effective upon filing these Articles of Merger in the Department of State,

_X_The plan of merger shall be effective on March 31, 2001 (Date) at 11:30 p.m. (Hour)

5. The manner in which the plan of merger was adopted by each domestic corporation is as follows:

Name of Corporation	Manner of Adoption
SmithKline Beecham Corporation	Adopted by the directors and shareholders pursuant to 15 Pa.C.S. § 1926(a).

6. (Strike out this paragraph if no foreign corporation is a party to the merger). The plan was authorized, adopted or approved, as the case may be, by the foreign business corporation (or each of the foreign business corporations) party to the plan in accordance with the laws of the jurisdiction in which it is incorporated.

7. (Check, and if appropriate complete, one of the following):

_X_The plan of merger is set forth in full in Exhibit A attached hereto and made a part hereof.

___Pursuant to 15 Pa.C.S. § 1901 (relating to omission of certain provisions from filed plans) the provisions, if any, of the plan of merger that amend or constitute the operative Articles of Incorporation of the surviving corporation as in effect subsequent to the effective date of the plan are set forth in full in Exhibit A attached hereto and made a part hereof. The full text of the plan of merger is on file at the principal place of business of the surviving corporation, the address of which is:

_____
Number and Street City State Zip County

IN TESTIMONY WHEREOF, the undersigned corporation or each undersigned corporation has caused these Articles of Merger to be signed by a duly authorized officer thereof this _____ day of March, 2001.

SMITHKLINE BEECHAM CORPORATION
(Name of Corporation)

By: Donald F. Parman
(Signature)

Name: Donald F. Parman, Secretary

GLAXO WELLCOME INC.
(Name of Corporation)

By: Paul A. Holcombe Jr.
(Signature)

Name: Paul A. Holcombe, Jr., Secretary

2801-0209X
PATENT

INVENTOR'S STATEMENT FOR PETITION TO CORRECT THE INVENTORSHIP OF A PATENT UNDER 37 C.F.R.§1.324

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, KAREN ELIZABETH LACKEY, have no disagreement with the proposed change in the inventorship of US Pat. Nos. 6,713,485 B2 and 6,727,256, whereby Kathryn Jane Smith will be deleted as a named inventor of the claimed subject matter.

By Karen Elizabeth Lackey
KAREN ELIZABETH LACKEY

Date July 15, 2005

2801-0209X
PATENT

INVENTOR'S STATEMENT FOR PETITION TO CORRECT THE INVENTORSHIP OF A PATENT UNDER 37 C.F.R.§1.324

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, KATHRYN JANE SMITH, have no disagreement with the proposed change in the inventorship of US Pat. Nos: 6,713,485 B2 and 6,727,256 whereby I will be deleted as a named inventor of the claimed subject matter.

By K. J. SMITH
KATHRYN JANE SMITH

Date 13th July 2005.

2801-0209X
PATENT

INVENTOR'S STATEMENT FOR PETITION TO CORRECT THE INVENTORSHIP OF A PATENT UNDER 37 C.F.R.§1.324

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, GEORGE STUART COCKERILL, have no disagreement with the proposed change in the inventorship of US Pat. Nos. 6,713,485 B2 and 6,727,256 whereby Kathryn Jane Smith will be deleted as a named inventor of the claimed subject matter.

By _____
GEORGE STUART COCKERILL

Date 22nd July 2005

2801-0209X
PATENT

INVENTOR'S STATEMENT FOR PETITION TO CORRECT THE INVENTORSHIP OF A PATENT UNDER 37 C.F.R.§1.324

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, MALCOLM CLIVE CARTER, have no disagreement with the proposed change in the inventorship of US Pat. Nos. 6,713,485 B2 and 6,727,256 whereby Kathryn Jane Smith will be deleted as a named inventor of the claimed subject matter.

By _____
MALCOLM CLIVE CARTER

Date 11th July 2005

2801-0209X
PATENT

INVENTOR'S STATEMENT FOR PETITION TO CORRECT THE INVENTORSHIP OF A PATENT UNDER 37 C.F.R.§1.324

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, STEPHEN BARRY GUNTRIP, have no disagreement with the proposed change in the inventorship of US Pat. Nos. 6,713,485 B2 and 6,727,256 whereby Kathryn Jane Smith will be deleted as a named inventor of the claimed subject matter.

By _____ Date 11/7/05
STEPHEN BARRY GUNTRIP

EXHIBIT 9A

IND diligence log

Regulatory Affairs
CARDS
View Manager Brief Report

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	GW572016 (EGFR/ErbB2 Tyrosine Kinase Inhibitor) Pre-IND Submission and Meeting Request	08-Aug-2000	Yes
GSK Correspondence	Pre-IND; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Pre-IND Submissions; Information Package	20-Sep-2000	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, Nonclinical Draft Responses to pre-IND questions	16-Oct-2000	Yes
GSK FAX/E-mail	Pre-IND; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Clinical	03-Nov-2000	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: CMC	07-Nov-2000	Yes
FDA FAX/E-mail	Pre-IND; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical	07-Nov-2000	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Initial Investigational New Drug Application: Protocol(s) Included Serial No.: 0000	06-Dec-2000	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls Serial No.: 0001	18-Dec-2000	Yes
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: CMC	19-Dec-2000	No
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Acknowledgement: IND # Assigned	21-Dec-2000	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical	28-Dec-2000	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, Protocol EGF10001	03-Jan-2001	Yes
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Protocol EGF10001	03-Jan-2001	No

Communication Type	Re Line	Date	Attachments?
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Clinical, Protocol EGF10001	04-Jan-2001	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, Nonclinical, IND Review Comments and Approval to Proceed	05-Jan-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol Response to FDA Request/Comment: Clinical Serial No.: 0002	12-Jan-2001	Yes
GSK Telephone Conversation	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Teleconference: Nonclinical, Final Toxicology Study Reports	16-Jan-2001	No
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, CMC, Nonclinical	31-Jan-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical, Study Reports Serial No.: 0003	05-Apr-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0004	01-May-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls Serial No.: 0005	15-May-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 0006	29-May-2001	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical	07-Aug-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	27-Aug-2001	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0007		
GSK Correspondence	General Correspondence Notification of Corporation Name Change	30-Aug-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol Serial No.: 0009	13-Sep-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical Serial No.: 0010	14-Sep-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls Serial No.: 0011	28-Sep-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Serial No.: 0012	05-Oct-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0013	18-Oct-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls Serial No.: 0014	14-Nov-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol Serial No.: 0015	15-Nov-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0016	26-Nov-2001	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol Serial No.: 0017	04-Dec-2001	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor	07-Dec-2001	Yes

Communication Type	Re Line	Date	Attachments?
	Comment/Information Request: Clinical, CMC, Protocol, Statistical		
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical, Study Reports Serial No.: 0018	16-Jan-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol Serial No.: 0019	19-Feb-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 0020	20-Feb-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Annual Report Serial No.: 0021	25-Feb-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 0022	01-Mar-2002	Yes
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Clinical Trials Data Bank	26-Apr-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0023	09-May-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls Serial No.: 0024	07-Jun-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF10024 Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol EGF10003 and EGF10004 Serial No.: 0025	10-Jul-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator	06-Aug-2002	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0026		
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 0027	23-Aug-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Clinical, Non-IND Protocols Serial No.: 0028	30-Aug-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol Amendment: Other, Transfer of Obligations to Contract Research Organization Seria	09-Sep-2002	Yes
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Clinical Trials Data Bank	02-Oct-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF10009 Protocol Amendment: New Investigator Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 0030	07-Oct-2002	Yes
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Clinical Trials Data Bank	22-Oct-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0031	31-Oct-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls Serial No.: 0032	31-Oct-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Written Safety Report Serial No.: 0033	05-Nov-2002	Yes

Communication Type	Re Line	Date	Attachments?
	pp.000001 - 000001.09		
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Safety; Initial 7-Day Report	11-Nov-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Written Safety Report Serial No.: 0034 pp.000001 - 000001.09	15-Nov-2002	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical	19-Nov-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0035	02-Dec-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 03 to EGF10004 and Amendments 01 to EGF20002 and EGF20004 Serial No.: 0036	10-Dec-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol for EGF10019 Protocol Amendment: New Investigator Serial No.: 0037	10-Dec-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Clinical Serial No.: 0038	17-Dec-2002	Yes
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Clinical Trials Data Bank	30-Dec-2002	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: CMC, Protocol	30-Dec-2002	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0039	08-Jan-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor	09-Jan-2003	Yes

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Initial Serial No.: 0040		
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: CMC, Meeting Request	10-Jan-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Meeting Request, CMC Serial No.: 0041	10-Jan-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 07 to Protocol EGF10003 Serial No.: 0042	28-Jan-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0043	31-Jan-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0044	04-Feb-2003	Yes
GSK Telephone Conversation	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Teleconference: CMC, Meeting Agenda or Details	05-Feb-2003	No
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Change in Regulatory Responsibility	06-Feb-2003	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Status Update	06-Feb-2003	No
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Nonclinical	07-Feb-2003	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Nonclinical	07-Feb-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Request to Postpone Meeting: CMC Serial No.: 0045	07-Feb-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor	11-Feb-2003	Yes

Communication Type	Re Line	Date	Attachments?
	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 0046		
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Amendment Serial No.: 0047	13-Feb-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Annual Report Serial No.: 0048	19-Feb-2003	Yes
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Safety	24-Feb-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Notification of Imminent Carcinogenicity Protocol for Special Protocol Assessment Serial No.: 0049	28-Feb-2003	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Protocol, Safety	03-Mar-2003	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical	03-Mar-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0050	04-Mar-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up, Initial Serial No.: 0053	14-Mar-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 2 for Protocol EGF10011 Serial No.: 0051	17-Mar-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0054	17-Mar-2003	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Serial No.: 0052	17-Mar-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Written Safety Report Serial No.: 0055 pp.000001 - 000001.08	18-Mar-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Request for End of Phase 2 Meeting (trastuzumab-refractory Breast Cancer) Serial No.: 0056	21-Mar-2003	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	24-Mar-2003	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	24-Mar-2003	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	25-Mar-2003	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	25-Mar-2003	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	26-Mar-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, EGF10010 Protocol Amendment: Change in Protocol, Amendment 2 Serial No.: 0057	26-Mar-2003	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	31-Mar-2003	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	31-Mar-2003	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor	31-Mar-2003	No

Communication Type	Re Line	Date	Attachments?
	General Memorandum: Meeting Agenda or Details		
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Carcinogenicity Submission	01-Apr-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator, Investigator Add Serial No.: 0058	01-Apr-2003	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	03-Apr-2003	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	03-Apr-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 2 for Protocol EGF20008 Serial No.: 0059	11-Apr-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up, Initial Serial No.: 0060	14-Apr-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, EGF10021 Protocol Amendment: Change in Protocol, Amendments 1 and 2 for EGF10021 Protocol Amendment: New Investigator for Protocol EGF10021 Serial No.: 0061	15-Apr-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Written Safety Report Serial No.: 0062 pp 000001 - 0000001.09	17-Apr-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Clinical Serial No.: 0064	23-Apr-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Serial No.: 0063	23-Apr-2003	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Serial No.: 0065	28-Apr-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 4 for Protocol EGF10004 Serial No.: 0066	07-May-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document for End of Phase 2 Meeting (trastuzumab-refractory breast cancer) Serial No.: 0067	08-May-2003	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Other; Request for a Electronic Copy of the Meeting Package	12-May-2003	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Food Effects	13-May-2003	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Copies of the Briefing Document for the Jun 12, 2003 Meeting	14-May-2003	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Copies of the Briefing Document for the Jun 12, 2003 Meeting	14-May-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0068	14-May-2003	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, Protocol EGF10011	16-May-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0069 pp.000001 - 000001.10	20-May-2003	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical	22-May-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up, Initial Written Safety Reports	23-May-2003	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0070 pp. 00001 - 00001.13		
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, Protocol	27-May-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 0071	27-May-2003	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Provided an Advanced Copy of the Submission Containing Information on Dose Justification for the Carcinogenicity Studies	29-May-2003	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Nonclinical; Carcinogenicity Studies	29-May-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Serial No.: 0072	29-May-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Nonclinical Request for Special Protocol Assessment - Carcinogenicity Protocol Serial No.: 0073	30-May-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Clinical - Response to FDA questions dated 27 May 2003 concerning protocols EGF 10011 and EGF 10021 Serial No.: 0074	02-Jun-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0075	03-Jun-2003	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request; Special Protocol Assessment	05-Jun-2003	No
GSK Trip Report	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Type: End of Phase II Meeting: Official Internal FDA Minutes from 6/5/2003 Meeting Held to Discuss GSK's Briefing Document for the 6/12/2003 End of Phase 2 meeting for GW572016 (IND 61,362)	05-Jun-2003	No

Communication Type	Re Line	Date	Attachments?
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	10-Jun-2003	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	10-Jun-2003	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	10-Jun-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical, Study Report Serial No.: 0076	10-Jun-2003	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: 6/5/2003 Internal FDA Type B - EOP2 Guidance Meeting to Discuss Proposed Indication: trastuzumab-refractory breast cancer	10-Jun-2003	No
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details IND 61,362 (GW572016) Meeting	10-Jun-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Written Safety Report Serial No.: 0077 pp 000001 - 000001.08	10-Jun-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0078	10-Jun-2003	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Series of Communications Regarding the Jun 12, 2003 Meeting	11-Jun-2003	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	11-Jun-2003	No
GSK Trip Report	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Type: End of Phase II Meeting	12-Jun-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 2 to Protocol EGF20002 Serial No.: 0079	13-Jun-2003	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Written Safety Report Serial No.: 0080 pp. 000001 - 000001.11	13-Jun-2003	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Draft Protocol, Nonclinical; Rodent Carcinogenicity Studies	17-Jun-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Clinical, Protocol Serial No.: 0082	20-Jun-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0081	20-Jun-2003	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Draft Protocol, Nonclinical; Rodent Carcinogenicity Protocols	23-Jun-2003	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Draft Protocol, Nonclinical; Rodent Carcinogenicity Studies	24-Jun-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Written Safety Report Serial No.: 0083 pp. 000001 - 000001.08	24-Jun-2003	Yes
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Clinical : Proposed Amendment to Protocol EGF20008	25-Jun-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Written Safety Report Serial No.: 0085 pp. 000001 - 000001.08	26-Jun-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Serial No.: 0084	27-Jun-2003	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Draft Protocol; Request for Guidance on EGF20008	07-Jul-2003	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0086	07-Jul-2003	Yes
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Minutes of Meeting for the 6/12/2003 Type B - End of Phase 2 Guidance Meeting	08-Jul-2003	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Draft Protocol EGF20008	11-Jul-2003	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment; Serial No. 082	11-Jul-2003	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Date and Serial Number Request for Protocol Submission	11-Jul-2003	No
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Clinical, Protocol	11-Jul-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls Color chang, Updated drug product specification Serial No.: 0087	14-Jul-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0088	16-Jul-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0089	22-Jul-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls Replacement page to correct error in Table 1 on page 3 of July 14, 2003 submission Serial No.: 0090	24-Jul-2003	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Request Status Update on Draft Protocol Outline for EGF20008	29-Jul-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls, CMC	30-Jul-2003	Yes

Communication Type	Re Line	Date	Attachments?
	Correcting error in Table 1 of the document regarding microcrystalline cellulose Serial No.: 0091		
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, Protocol	05-Aug-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, EGF30008 Serial No.: 0093	19-Aug-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Clinical Request for Special Protocol Assessment - Clinical Protocol Serial No.: 0092	26-Aug-2003	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: GSK Inquired as the the Receipt of the Special Protocol Assessment Submission for Protocol EGF100151	03-Sep-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; EGF10010, Amendment 1 Serial No.: 0095	03-Sep-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF10012 Serial No.: 0094	03-Sep-2003	Yes
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Acknowledgement: Receipt of 8/26/2003 Request for Special Protocol Assessment	04-Sep-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 0096	05-Sep-2003	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Additional Copies of Special Protocol Assessment	08-Sep-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Desk Copies of Special Protocol Assessment Request	09-Sep-2003	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Special Protocol Assessment; Review Period	11-Sep-2003	No

Communication Type	Re Line	Date	Attachments?
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Special Protocol Assessment Copies Received	11-Sep-2003	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the No 24, 2003 Pre-NDa Meeting	12-Sep-2003	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Special Protocol Assessment; Review Policy	12-Sep-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical; Amendment 001 to Protocol EGF10012 Serial No.: 0099	12-Sep-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 001 for EGF10023 Serial No.: 0098	12-Sep-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol Serial No.: 0097	12-Sep-2003	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, Protocol EGF100151	15-Sep-2003	No
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Copy of Aug 25, 2003 Cover Letter for the Request for Special Protocol Assessment Submission	15-Sep-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0100	16-Sep-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Nonclinical - Special Protocol Assessment Carcinogenicity Protocol (mouse) Serial No.: 0101	17-Sep-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Nonclinical - Special Protocol Assessment Carcinogenicity Protocol (rat) Serial No.: 0102	17-Sep-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor	19-Sep-2003	Yes

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Initial Serial No.: 0103		
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0104	23-Sep-2003	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Protocol: Special Protocol Assessment Review	24-Sep-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendments 3 & 4 for EGF10021 Serial No.: 0106	25-Sep-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol: EGF100262 Serial No.: 0105	25-Sep-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Other - Request for Fast Track Designation Serial No.: 0107	29-Sep-2003	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Nonclinical; Was the Mouse Pilot Carcinogenicity Study, M41011, Submitted Previously to the IND?	06-Oct-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical Serial No.: 0108	10-Oct-2003	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request; GSK to Provide the Usual Three Desk Copies of the N-101 Mouse Study	14-Oct-2003	No
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Acknowledgement: Fast Track Designation	14-Oct-2003	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Status Update; Goal Date Extended for Mouse Study	20-Oct-2003	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Special Protocol Assessment for a Carcinogenicity Protocol	20-Oct-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor	21-Oct-2003	Yes

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Follow-up Serial No.: 0109		
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Nonclinical; Discussion of the Speical Protocol Assessment for the Rat Carcinogenicity Study	22-Oct-2003	No
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Fast Track Designation	28-Oct-2003	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Nonclinical Response to Carcinogenicity Protocol Assessment Request	30-Oct-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0110	05-Nov-2003	Yes
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Clinical:GSK Wil Not Pursue a Prior Approval Supplement for the Metastatic Breast Cancer Study of GW572016 and Paclitaxel	07-Nov-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Written Safety Report Serial No.: 0111	07-Nov-2003	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Statistical	13-Nov-2003	Yes
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Protocol: Status of Special Protocol Assessment	17-Nov-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol: EGF10021, Amendment 3 Serial No.: 0112	17-Nov-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol: EFG10032 Serial No.: 0113	20-Nov-2003	Yes
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Response to Special Protocol Assessment Request	21-Nov-2003	Yes

Communication Type	Re Line	Date	Attachments?
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical	21-Nov-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Letter of Authorization Serial No.: 0114	25-Nov-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Meeting Agenda or Details, Meeting Request Serial No.: 0116	26-Nov-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Written Safety Report Serial No.: 0115	26-Nov-2003	Yes
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Meeting Request for Transitional Cell Carcinoma of the Bladder	02-Dec-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0119	04-Dec-2003	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the Feb 5, 2004 Meeting	09-Dec-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Clinical, Other Serial No.: 0121	09-Dec-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Information for Protocols EGF10012, EGF10023, EGF10030, EGF20002, EGF20004, EGF20008 and EGF20014 Serial No.: 0120	09-Dec-2003	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0122	11-Dec-2003	Yes
GSK Telephone Conversation	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 7-Day Safety Report	22-Dec-2003	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor	23-Dec-2003	Yes

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Initial Serial No.: 0123		
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document for End of Phase 2 Meeting (Transitional Cell Carcinoma of the Bladder) Serial No.: 0124	07-Jan-2004	Yes
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: GSK Will Send Information Requested in FDA's Jan 12, 2004 Email	12-Jan-2004	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Requested a Copy of the Background, Cover Letter, and Questions on a Disc/CD or by Email for the EOP2 meeting	12-Jan-2004	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0126	12-Jan-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: Protocol EGF30001 Enrollment Criteria Serial No.: 0125	12-Jan-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical, Study Reports Serial No.: 0127	14-Jan-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol EGF10021: Amendment 005 Serial No.: 0128	22-Jan-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical; Amendment 001 for EGF10030 Serial No.: 0129	29-Jan-2004	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum; Draft Responses for Feb 5, 2004	03-Feb-2004	No
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details	04-Feb-2004	No
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor	04-Feb-2004	No

Communication Type	Re Line	Date	Attachments?
	General Memorandum: Meeting Agenda or Details		
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation for Protocols EGF10021, EGF10030, EGF10032, EGF20002, EGF20004, EGF20008, EGF20014, EGF30001, EGF30008, EGF100151 Serial No.: 0130	06-Feb-2004	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Pharmaockinetic Analysis and Protocol EGF100262	09-Feb-2004	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Pharmacokinetic Analysis	09-Feb-2004	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical; FDA Responses to GSK's Questions Submitted as Part of a Meeting Briefing Document for an End of Phase 2 Meeting	10-Feb-2004	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol EGF10009, Clinical; Amendments 1,2 and 3 Serial No.: 0132	11-Feb-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol EGF20014, Clinical; Amendment 1 Serial No.: 0131	11-Feb-2004	Yes
FDA Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Minutes of Meeting: Feb 5, 2004 End of Phase II Meeting	12-Feb-2004	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Clinical, Request Status Update; Response to FDA Comments on Carc Studies (30 October 2003)	17-Feb-2004	No
GSK FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Nonclinical	17-Feb-2004	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0134	20-Feb-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0133	20-Feb-2004	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0136	25-Feb-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Annual Report: Adverse Event Summary, Clinical Study Information, Investigational Plan Period Covering Dec 6, 2002 Through Dec 5, 2003 Serial No.: 0135	25-Feb-2004	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Clinical; Recent Meeting	26-Feb-2004	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence - Response to FDA Request for Information Serial No.: 0137	01-Mar-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0138	03-Mar-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0139	04-Mar-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0140	10-Mar-2004	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical Pharmacology and Biopharmaceutics Review Comments	11-Mar-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol EGF20008, Amendments 3 and 4 Serial No.: 0141	11-Mar-2004	Yes
GSK Telephone Conversation	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 7-Day Safety Report	18-Mar-2004	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Clinical	19-Mar-2004	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor	24-Mar-2004	Yes

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Initial Serial No.: 0144		
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0143	24-Mar-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Correspondence: CMC, Meeting Request Serial No.: 0142	24-Mar-2004	Yes
GSK Telephone Conversation	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 7-Day Safety Report	26-Mar-2004	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0146	29-Mar-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 03 for Protocol EGF10009 Serial No.: 0145	29-Mar-2004	Yes
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details, CMC	31-Mar-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0147	31-Mar-2004	Yes
GSK Telephone Conversation	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 7-Day Safety Report	07-Apr-2004	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0148	07-Apr-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0149	14-Apr-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial	16-Apr-2004	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0150		
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendments 1 and 2 for Protocol EGF30001 Serial No.: 0151	20-Apr-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical, Study Report Serial No.: 0152	23-Apr-2004	Yes
FDA FAX/E-mail	IND 65,747; GW786034 (VEGFR Tyrosine Kinase Inhibitor) IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Lead IND, etc.	26-Apr-2004	No
FDA FAX/E-mail	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical Pharmacology	26-Apr-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0154	26-Apr-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0153	26-Apr-2004	Yes
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0155	27-Apr-2004	Yes
GSK Telephone Conversation	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor General Teleconference: CMC	03-May-2004	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, EGF10027 Protocol Amendment: Change in Protocol, Amendment 001 to EGF10027 Protocol Amendment: New Investigator for EGF10027 Amendment: Other, Transfer of Ob	03-May-2004	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report: Safety	04-May-2004	No
GSK Correspondence	IND 61,362; GW572016 (EGFR/ErbB2) Tyrosine Kinase Inhibitor	05-May-2004	Yes

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Follow-up Serial No.: 0157		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment for Protocol EGF100151 Serial No.: 0159	06-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator, Investigator Add Protocol Amendment: New Investigator, Other 1572 Change Serial No.: 0158	07-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0160	10-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 0161	13-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization for the Division of Cancer Treatment and Diagnosis Serial No.: 0163	17-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF20009 Protocol Amendment: New Investigator Serial No.: 0162	17-May-2004	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: CMC, Meeting Agenda or Details Additional information for May 19, 2004 telecon	18-May-2004	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical; Amendments 1 and 2 for Protocol EGF100151 Serial No.: 0164	19-May-2004	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Teleconference: Meeting Agenda or Details	21-May-2004	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial	21-May-2004	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0165		
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: CMC-The purpose of this End of Phase 2 Meeting (Meeting Minutes)	24-May-2004	No
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of May 19, 2004 Guidance Meeting	25-May-2004	Yes
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of Meeting: End of Phase II Meeting, CMC	25-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 002 for Protocol EGF10023 Serial No.: 0166	26-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical, Study Report Serial No.: 0167	27-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0172	28-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0171	28-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0170	28-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Nonclinical Request for Special Protocol Assessment - Rat Carcinogenicity Protocol Serial No.: 0168	28-May-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Nonclinical Request for Special Protocol Assessment - Mouse Carcinogenicity Protocol Serial No.: 0169	28-May-2004	Yes
GSK Telephone	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	01-Jun-2004	No

Communication Type	Re Line	Date	Attachments?
Conversation	7-Day Safety Report		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0176	02-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0175	02-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol EGF30008, Amendment 001 Serial No.: 0174	02-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of Meeting: End of Phase II Meeting, CMC Serial No.: 0177	03-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0178	04-Jun-2004	Yes
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Acknowledgement of the May 28, 2004 Request for a Special Rat Carcinogenicity Protocol	07-Jun-2004	Yes
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Acknowledgement of May 28, 2004 Request for a Special Mouse Carcinogenicity Protocol Assessment	07-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0179	07-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0181	09-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0180	09-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator, Investigator Add	14-Jun-2004	Yes

Communication Type	Re Line	Date	Attachments?
	Protocol Amendment: New Protocol, SR30995, Flavor Development Protocol Serial No.: 0173		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0182	15-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0184	16-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0183	16-Jun-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator, Investigator Add Protocol Amendment: New Protocol, EGF19060 Serial No.: 0185	01-Jul-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0186	02-Jul-2004	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Nonclinical Response to Carcinogenicity Protocol Assessment Request - Final CAC Report	08-Jul-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol: EGF10014 Protocol Amendment: New Investigator Serial No.: 0187	08-Jul-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol EGF10018, Amendment 001 Serial No.: 0188	12-Jul-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0189	14-Jul-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	19-Jul-2004	Yes

Communication Type	Re Line	Date	Attachments?
	Protocol Amendment: Change in Protocol EGF30001, Amendment 003 Serial No.: 0190		
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum; Emergency IND request for Patient (Lapatinib, GW572016)	20-Jul-2004	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Request FDA Guidance Serial No.: 0191	21-Jul-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 01 for EGF10014, 02 for EGF20014, 03 for EGF30001 and 03 for EGF100151 Serial No.: 0192	29-Jul-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0193	30-Jul-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0194	02-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0196	05-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0195	05-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Clinical, Study Reports for Protocols EGF10001, EGF10002, EGF10008, EGF10013, EGF10018 and EGF10024 Serial No.: 0197	13-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0199	16-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0198	16-Aug-2004	Yes

Communication Type	Re Line	Date	Attachments?
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	16-Aug-2004	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 005 for EGF20008 and Amendment 003 for EGF100151 Serial No.: 0200	17-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0201	18-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0202	20-Aug-2004	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	23-Aug-2004	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0203	24-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0204	25-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0206	26-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0205	26-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls, Response Requested Serial No.: 0207	31-Aug-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0208	01-Sep-2004	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0212	03-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0211	03-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0210	03-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0209	03-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0214	07-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation EGF10004, EGF10021, EGF10023, EGF10027, EGF10030, EGF10032, EGF19060, EGF20008, EGF20009, EGF20014, EGF30001, EGF30008 and EGF100151	07-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0215	08-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0218	13-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0217	13-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0216	13-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up	21-Sep-2004	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0219		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0220	23-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0221	28-Sep-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0222	30-Sep-2004	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Request Status Update; IND 61,362 Request for FDA Guidance	05-Oct-2004	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0225	05-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0224	05-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol: Amendment 004 to Protocol EGF100151 Serial No.: 0223	05-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0226	06-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation for Protocols EGF10023, EGF10027, EGF20002, EGF20004, EGF20008, EGF20009, EGF20014, EGF30001 and EGF30008 Serial No.: 0227	07-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0229	11-Oct-2004	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0228	11-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0233	15-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0232	15-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0231	15-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0230	15-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0237	18-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0236	18-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0235	18-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0239	20-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0238	20-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up	21-Oct-2004	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0240		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0242	22-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0241	22-Oct-2004	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Protocol EGF10018; RE IND 61,362 #188	26-Oct-2004	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to CMC question	26-Oct-2004	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	27-Oct-2004	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0243	27-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0244	28-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0246	29-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0245	29-Oct-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0248	03-Nov-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0247	03-Nov-2004	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0250	09-Nov-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0249	09-Nov-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0251	12-Nov-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls, Response Requested Serial No.: 0252	22-Nov-2004	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	23-Nov-2004	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0254	24-Nov-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0253	24-Nov-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0255	30-Nov-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0258	01-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0257	01-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0256	01-Dec-2004	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0259	03-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0261	06-Dec-2004	Yes
GSK Correspondence	IND 65,747; GW786034 (VEGFR Tyrosine Kinase Inhibitor) Serial No.: 0026 IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Serial No.: 0260 15-Day ADR Report: Initial	06-Dec-2004	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, Protocol, Statistical	07-Dec-2004	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol: Amendment 6 to Protocol EGF20008 Serial No.: 0263	07-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0262	07-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0266	09-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0264	09-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 5 to Protocol EGF100151 Serial No.: 0265	09-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical Request for Special Protocol Assessment: Carcinogenicity Serial No.: 0268	10-Dec-2004	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0267	10-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0270	13-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0269	13-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0272	14-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0271	14-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0273	15-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0274	20-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0277	21-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0276	21-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0275	21-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up	23-Dec-2004	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0280		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0279	23-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0278	23-Dec-2004	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0283	03-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0282	03-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0281	03-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0284	05-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, EGF102587 Protocol Amendment: Change in Protocol, Amendment 001 to Protocol EGF102857 Protocol Amendment: New Investigator Amendment: Other, Transfer of Oblig	06-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0286	10-Jan-2005	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	11-Jan-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0287	14-Jan-2005	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0289	17-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0288	17-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocols: Amendment 2 to Protocol EGF30001 and Amendment 4 to Protocol EGF30008 Serial No.: 0290	17-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 0291	18-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0292	19-Jan-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Safety	24-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0294	24-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0293	24-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0295	26-Jan-2005	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	26-Jan-2005	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Other, Response to Serial Number 0252	27-Jan-2005	No
GSK Telephone	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	27-Jan-2005	No

Communication Type	Re Line	Date	Attachments?
Conversation	7-Day Safety Report		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0296	27-Jan-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Meeting Request Serial No.: 0297	31-Jan-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Safety	01-Feb-2005	Yes
FDA Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor FDA Communication on Lapatinib - FDA Meeting Granted	01-Feb-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0299	01-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0298	01-Feb-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the Mar 31, 2005 End of Phase 2 Meeting	02-Feb-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the Mar 31, 2005 End of Phase 2 Meeting	02-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0300	02-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment 002 for Protocol EGF10027 Serial No.: 0301	02-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0305	07-Feb-2005	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0304	07-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0303	07-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0302	07-Feb-2005	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	08-Feb-2005	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	08-Feb-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0306	09-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0309	10-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0308	10-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0307	10-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigators for Protocols EGF10003, EGF10027, EGF10030, EGF19060, EGF20002, EGF20008, EGF20009, EGF20014, EGF30001, EGF10051 and EGF30008 Serial No.: 0310	11-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0311	14-Feb-2005	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0313	15-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0312	15-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0315	16-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0314	16-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0317	17-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0316	17-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls, Response Requested Serial No.: 0318	18-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, Clinical Protocol Amendment: Change in Protocol, Clinical Protocol Amendment: New Investigator Amendment: Other, Transfer of Obligations to Contract Research	22-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 2 to Protocol EGF10005 Serial No.: 0320	22-Feb-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the Mar 31, 2005 Meeting	23-Feb-2005	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	25-Feb-2005	No

Communication Type	Re Line	Date	Attachments?
	General Memorandum: Meeting Agenda or Details for Mar 31, 2005 Meeting		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0322	25-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document for the Mar 31, 2005 Meeting to Discuss the Treatment of Patients With Advanced or Metastatic Breast Cancer Serial No.: 0321	28-Feb-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0323	01-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0324	02-Mar-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Provided a Copy of the Questions for the Division and Specifically Formatted Information Requested (i.e., Overall Development Plan and Protocol Outlines).	03-Mar-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Annual Report Covering the Period From Dec 6, 2003 Through Dec 5, 2004 Serial No.: 0325	04-Mar-2005	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	08-Mar-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0326	09-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0329	10-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0328	10-Mar-2005	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0327	10-Mar-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical; Clinical Parmacology and Biopharmaceutics Comments Regarding EGF102587	14-Mar-2005	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	14-Mar-2005	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	14-Mar-2005	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	14-Mar-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0331	14-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF102580 Protocol Amendment: Change in Protocol, Amendment 001 to Protocol EGF102580 Protocol Amendment: New Investigator Amendment: Other, Transfer of Obliga	14-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0332	15-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0335	16-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0334	16-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0333	16-Mar-2005	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0336	17-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0339	18-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0338	18-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0337	18-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0340	21-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0342	22-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0341	22-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0343	24-Mar-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details: Provided a List of Meeting Participants for the Mar 31, 2005 Meeting	25-Mar-2005	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical: Comments From Review Team Regarding the Jul 8, 2004 Submission (Serial No 187)	25-Mar-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical	29-Mar-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	30-Mar-2005	No

Communication Type	Re Line	Date	Attachments?
	General Memorandum: Meeting Agenda or Details: Provided a Revised List of GSK Attendees		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0344	30-Mar-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Safety Serial No.: 0345	30-Mar-2005	Yes
GSK Trip Report	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Topic: Clinical, Protocol: Minutes of FDA Meeting on Lapatinib (Metastatic Breast Cancer - 31 March 2005)	31-Mar-2005	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details: FDA Provided a List of Mar 31, 2005 Meeting Attendees	01-Apr-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0347	04-Apr-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0346	04-Apr-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Request for Guidance on Submitting Tradenames	05-Apr-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Request	05-Apr-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation for Protocols EGF10027, EGF20008, EGF20014 EGF30001, EGF30008 and EGF100151 Serial No.: 0348	05-Apr-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: FDA Provided Guidance on How to Submit Trade Name Proposals	07-Apr-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0349	07-Apr-2005	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, EGF104388 Serial No.: 0350	07-Apr-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor IND 65,747; GW786034 (VEGFR Tyrosine Kinase Inhibitor) Comment/Information Request: Safety	08-Apr-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0351	11-Apr-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Clinical: Provided a 3-Page List of Clinical Pharmacology/Biopharmaceutics Studies Originally Sent to the IND 6 May 2004 (Serial No. 159).	14-Apr-2005	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details: Rescheduling the Apr 14, 2005 Meeting	14-Apr-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0353	18-Apr-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0352	18-Apr-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0354	19-Apr-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details: GSK Provided the Slides Used at the Mar 31, 2005 Meeting and Also Updated the FDA on the Submission of the Special Protocol Assessment	22-Apr-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Clinical	22-Apr-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0356	26-Apr-2005	Yes

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0355	26-Apr-2005	Yes
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of Meeting: Mar 31, 2005 End of Phase II Meeting Held to Discuss the Early Results of EGF10023 and the Clinical Plan That Will Be Used to Support the NDA Application	29-Apr-2005	No
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of Meeting: Mar 31, 2005 End of Phase II Meeting Held to Discuss the Early Results of Study EGF10023 and to Discuss the Clinical Plan for Lapatinib That Will Be Used to Support an NDA Ap	29-Apr-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0357	02-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0360	03-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0359	03-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0358	03-May-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, Protocol FDA Provided Comments Regarding GSK's Planned Study of Lapatinib in Healthy Volunteers	05-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0363	09-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0362	09-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization	09-May-2005	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0361		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 001 for Protocol EGF20009 Serial No.: 0364	11-May-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: CMC; FDA Provided a Comment Regarding the Feb 18, 2005 Submission Suggesting That the 120 Count 200cc Bottle Be Used to Generate Stability Data	12-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0366	12-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0365	12-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0367	17-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0369	19-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0368	19-May-2005	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	20-May-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0370	20-May-2005	Yes
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Corrected Minutes of the Mar 31, 2005 Meeting	23-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial	23-May-2005	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0373		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0372	23-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0371	23-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 0374	25-May-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: End of Phase 2 Meeting Request	27-May-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Request for Type A End of Phase 2 Meeting (teleconference) (Metastatic Breast Cancer) Serial No.: 0375	27-May-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details; Scheduled a Tentative Meeting Date of Jul 25, 2005	31-May-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Protocol'; Provided an NCI protocol (CALBG Protocol 40302) as a Candidate for Possible Special Protocol Assessment	31-May-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Clinical: GSK interactions with Dr. Goodsaid Regarding Biomarkers	01-Jun-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0376	01-Jun-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Protocol: FDA Wanted to Know If the NCI Clinical Trial Had Begun Already	03-Jun-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Nonclinical	03-Jun-2005	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0377	06-Jun-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Nonclinical	07-Jun-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Nonclinical; Special Protocol Assessment Mouse Carcinogenicity Protocol Serial No.: 0378	07-Jun-2005	Yes
FDA Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Special Protocol Assessment - Appropriate: Carcinogenicity FDA Will Review CTEP Lapatinib (IND 61,362) Protocol as a Special Protocol Assessment.	09-Jun-2005	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Nonclinical	09-Jun-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigators for Protocols EGF10023, EGF10027, EGF102580 EGF103009, EGF19060, EGF20008, EGF20009, EGF20014, EGF30001, EGF30008 and EGF100151 Serial No.: 037	10-Jun-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence - Request for Preliminary Clearance of Proposed Proprietary Drug Name Serial No.: 0380	14-Jun-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0381	16-Jun-2005	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Teleconference: Teleconference Minutes; FDA Seminar on Pharmacogenomics in Cancer Drug Development	17-Jun-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Request for End of Phase 2 Meeting (ErbB2 Overexpressing Breast Cancer Brain Metastases) Serial No.: 0383	24-Jun-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	24-Jun-2005	Yes

Communication Type	Re Line	Date	Attachments?
	General Correspondence: Briefing Document (Metastatic Breast Cancer) Scheduled Jul 25, 2005 Meeting Serial No.: 0382		
FDA Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Teleconference: Meeting Agenda or Details; FDA Meeting on Lapatinib and Brain Mets (IND 61,362)	27-Jun-2005	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for Aug 4, 2005 Type A Meeting	28-Jun-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0384	28-Jun-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0385	30-Jun-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0388	01-Jul-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0387	01-Jul-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document Document (ErbB2 Overexpressing Breast Cancer Brain Metastases) Scheduled Jun 24, 2005 Meeting Serial No.: 0386	01-Jul-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details; Provided Questions for Aug 4th Meeting on Brain Metastases	05-Jul-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details; Provided Questions for Jul 25th Meeting on Metastatic Breast Cancer	05-Jul-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0389	06-Jul-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	13-Jul-2005	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Initial Serial No.: 0390		
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details; Upcoming Meetings Regarding IND 61,362	14-Jul-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0393	18-Jul-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0392	18-Jul-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0391	18-Jul-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence - Briefing Document (ErbB2 Overexpressing Breast Cancer Brain Metastases) Additional Information Serial No.: 0395	21-Jul-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation for Protocols EGF102580, EGF103009, EGF20008, EGF20009, EGF20014, EGF30001, EGF30008 and EGF100151 Serial No.: 0394	21-Jul-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the Jul 25, 2005 Meeting	25-Jul-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence - Request for Type A End of Phase 2 Meeting (Teleconference) (Metastatic Breast Cancer) Serial No.: 0397	26-Jul-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0396	26-Jul-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence - Background for Type A End of Phase 2 Meeting	29-Jul-2005	Yes

Communication Type	Re Line	Date	Attachments?
	(teleconference) (Metastatic Breast Cancer) Serial No.: 0399		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 005 to Protocol EGF30001 Serial No.: 0398	29-Jul-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for Sep 1, 2005 Meeting in Response to GSK's Jul 26, 2005 Meeting Request- -Date Correction	01-Aug-2005	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for Sep 1, 2005 Meeting in Response to GSK's Jul 26, 2005 Meeting Request	01-Aug-2005	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: FDA Provided Draft Responses to GSK's Jul 1, 2005 Questions	01-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, Clinical, EGF100161 Protocol Amendment: New Investigator for Protocol EGF100161 Serial No.: 0400	01-Aug-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Provided FDA With a Copy of the Jul 21, 2005 Briefing Document Addendum	03-Aug-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Clinical; EGF104900 Eligibility Criteria	05-Aug-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Slide from Jul 25, 2005 Meeting	05-Aug-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment; Slide Set From the Aug 4, 2005 Meeting	08-Aug-2005	No
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of Meeting: Jul 25, 2005 End of Phase II Meeting Held to Discuss Revised Phase 3 Clinical Trial Designs Aimed at Demonstrating the Activity of Lapatinib in Combination with Trastuzumab	08-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0401	10-Aug-2005	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation for Protocols EGF20008, EGF20009, EGF20014, EGF30001, EGF30008 and EGF100151 Serial No.: 0402	11-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0403	12-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Request by Swedish Cancer Institute Re: GW572016 Clinical Study (IND#72,323)	15-Aug-2005	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	17-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0406	19-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0405	19-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0404	19-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 006 to Protocol EGF100151 Serial No.: 0407	19-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0408	22-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0409	24-Aug-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for Sep 1, 2005 Meeting	25-Aug-2005	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0412	26-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0411	26-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0410	26-Aug-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0413	29-Aug-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical, Protocol: Eligibility Criteria for Protocol EGF104900	30-Aug-2005	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum; Cancel Meeting Thursday on IND 61,362	30-Aug-2005	No
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of Aug 4, 2005 Meeting Held to Discuss the Early Results of a Phase I Clinical Study EGF10023	02-Sep-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0415	02-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0414	02-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0416	07-Sep-2005	No
GSK Correspondence	IND 65,747; GW786034 (VEGFR Tyrosine Kinase Inhibitor) Serial No.: 0043 IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Serial No.: 0417 IND 69,184; GW786034 (VEGFR Tyrosine Kinase Inhibitor) - AMD	08-Sep-2005	No

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0008 15-Day ADR Report: Init		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0418	12-Sep-2005	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	14-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0421	15-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0420	15-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0419	15-Sep-2005	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	19-Sep-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Request Status Update: Proposed Tradename for Lapatinib (IND 61,362)	21-Sep-2005	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	21-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0423	21-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0422	21-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, EGF102980 Protocol Amendment: Change in Protocol. Amendment 001 to EGF102980	21-Sep-2005	Yes

Communication Type	Re Line	Date	Attachments?
	Protocol Amendment: New Investigator Serial No.: 0424		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation Serial No.: 0425	22-Sep-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0427	23-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0426	23-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0429	26-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0428	26-Sep-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0434	04-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0433	04-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0432	04-Oct-2005	No
GSK Correspondence	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) Serial No.: 0050 IND 69,184; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) - AMD Serial No.: 0010 IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Serial No.: 0431 1	04-Oct-2005	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0430	04-Oct-2005	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Request Status Update Review of Proposed Trade Name	07-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0437	07-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0436	07-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical: Eleven Nonclinical Study Reports Serial No.: 0435	07-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, EGF10015 Protocol Amendment: New Investigator Serial No.: 0441	10-Oct-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0440	10-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0439	10-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence - Status of Work Related to Genetic Impurity Serial No.: 0438	10-Oct-2005	Yes
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Status Update Proposed Trade Name Review	11-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	12-Oct-2005	No

Communication Type	Re Line	Date	Attachments?
	Protocol Amendment: New and Revised Investigator Documentation Serial No.: 0442		
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	14-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0446	18-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0445	18-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0444	18-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0443	18-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0447	21-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 002 for Protocols EGF102980 and EGF103009 Serial No.: 0448	24-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF104900 Protocol Amendment: New Investigator Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 0449	25-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF104383 Protocol Amendment: New Investigator Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 0450	27-Oct-2005	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical Serial No.: 0451	28-Oct-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0453	01-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0452	01-Nov-2005	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report: Safety	07-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0456	07-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0455	07-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0454	07-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 003 to Protocol EGF30008 Serial No.: 0457	10-Nov-2005	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0459	11-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation Serial No.: 0458	11-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0463	16-Nov-2005	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0462	16-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0461	16-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0460	16-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol and Amendment 001 for EGF105084 Protocol Amendment: New Investigator Serial No.: 0464	17-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0466	21-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0465	21-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0467	28-Nov-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0468	02-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0469	05-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0471	07-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	07-Dec-2005	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Follow-up Serial No.: 0470		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0472	09-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Request for Type B End of Phase 2 Meeting to Discuss the Development of Lapatinib as Adjuvant Therapy of Patients with Resectable SCCHN (Squamous Cell Carcinoma of the H	12-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation Serial No.: 0473	12-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0476	14-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0475	14-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF104334 Protocol Amendment: New Investigator Serial No.: 0477	19-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Request for Type B End of Phase 2 Meeting (Adjuvant Therapy of Early, ErbB2-overexpressing/amplified Breast Cancer) Serial No.: 0479	20-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0478	20-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0481	22-Dec-2005	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0480	22-Dec-2005	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	23-Dec-2005	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0483	03-Jan-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0482	03-Jan-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the Feb 22, 2006 Meeting Regarding Lapatinib for Early Breast Cancer in Response to GSK's Dec 21, 2005 Request	05-Jan-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the Feb 15, 2006 Meeting Regarding Lapatinib for Head and Neck Cancer in Response to GSK's Dec 14, 2005 Request	05-Jan-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 002 to Protocol EGF105084 Serial No.: 0485	06-Jan-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0484	06-Jan-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: FDA Questions Regarding S-457	09-Jan-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF104535 Protocol Amendment: New Investigator Serial No.: 0487	09-Jan-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical: Special Toxicity Study Reports Serial No.: 0486	09-Jan-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0488	11-Jan-2006	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0491	17-Jan-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0490	17-Jan-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document Scheduled Feb 15, 2006 Meeting Serial No.: 0489	18-Jan-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: CMC, Request for Participation in FDA Quality Assessment Pilot Program Docket No.: 2005N-0262	18-Jan-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Questions and Scheduling Details for the Feb 15, 2006 Meeting	19-Jan-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0492	19-Jan-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document for Type B End of Phase 2 Meeting (Adjuvant Therapy of Early, ErbB2-overexpressing Breast Cancer) Serial No.: 0493	25-Jan-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: GSK Will Provide Responses to FDA's Comments Regarding EGF30008	30-Jan-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request; FDA Requested Responses to Their Concerns RE: EGF30008 (S-457)	30-Jan-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum; New Contact Person at FDA	31-Jan-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0494	31-Jan-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	03-Feb-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: FDA Has Additional Questions Regarding S-457	06-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence - Revised Study Proposal for Type B End of Phase 2 Meeting (Squamous Cell Carcinoma of the Head and Neck) Serial No.: 0498	06-Feb-2006	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0497	06-Feb-2006	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0496	06-Feb-2006	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0495	06-Feb-2006	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	06-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0499	07-Feb-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	09-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0502	10-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	10-Feb-2006	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Follow-up Serial No.: 0501		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0500	10-Feb-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Faxing Draft Minutes for Feb 15, 2006 Meeting	14-Feb-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details; Meeting Attendees for the Feb 15, 2006 Meeting	14-Feb-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: FDA Provided Draft Responses to Questions Submitted in the Jan 18, 2006 Briefing Document for the Upcoming Feb 15, 2006 Meeting	14-Feb-2006	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0507	14-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0506	14-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0505	14-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0504	14-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation Serial No.: 0508	14-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls: RESPONSE REQUESTED Serial No.: 0503	14-Feb-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	16-Feb-2006	No

Communication Type	Re Line	Date	Attachments?
	Response to FDA Request/Comment: GSK's Response to FDA's Comments on S-457 Will Be Sent Next Week		
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: GSK Responses to FDA Regarding S-457	16-Feb-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: FDA Is Okay with Timeline for Receipt of GSK's Response to Their Comments on S-457	20-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0511	20-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0510	20-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0509	20-Feb-2006	No
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of Feb 15, 2006 End of Phase II Meeting	27-Feb-2006	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Clinical, Study Report (Protocol EGF10032) Serial No.: 0513	28-Feb-2006	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Clinical, Study Report (Protocol EGF10012) Serial No.: 0512	28-Feb-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0514	01-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Response to FDA Questions Regarding Amendment to Protocol EGF30008 submitted to IND 61,362 (Serial No. 0457) Serial No.: 0516	03-Mar-2006	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Annual Report Covering the Period From Dec 6, 2004 Through Dec 5, 2005	03-Mar-2006	Yes

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0515		
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of Feb 22, 2006 End of Phase II Meeting	07-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0517	08-Mar-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: CMC: Request for Feedback on Drug Substance Revision to Reduce Genotoxic Impurity	09-Mar-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Statistical; FDA Provided a Response to GSK's Question On How to Define the ITT Population in Phase 3 Studies	09-Mar-2006	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: CMC; Request for Feedback on a Synthesis Revision Needed to Reduce the Level of Genotic Impurity in the Drug Substance	10-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0518	10-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0520	14-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0519	14-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Request for Type B End-of-Phase 2 Meeting; Treatment of Relapsed, ErbB2-Overexpressing/Amplified Inflammatory Breast Cancer and ErbB2-Overexpressing Breast Cancer Brain Me	15-Mar-2006	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0521	15-Mar-2006	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	20-Mar-2006	No

Communication Type	Re Line	Date	Attachments?
	General Memorandum: Meeting Request for a Meeting to Discuss Interim Results from Protocol EGF100151		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Request for Special Protocol Assessment Draft Protocol CALGB 40302 Serial No.: 0523	20-Mar-2006	Yes
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the Mar 23, 2006 Teleconference	21-Mar-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Request for a Meeting to Discuss Stopping Enrollment to Protocol EGF100151	21-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0524	21-Mar-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for Mar 23, 2006 Teleconference	22-Mar-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Teleconference: CMC, Request Status Update on Feb 14, 2006 Serial 503	22-Mar-2006	No
GSK Trip Report	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Topic: Clinical Study EGF100151	23-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0527	28-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0526	28-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0525	28-Mar-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Requested Final Minutes From the Feb 15, 2006 Meeting	30-Mar-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the May 16, 2006 Type B End	30-Mar-2006	Yes

Communication Type	Re Line	Date	Attachments?
	of Phase 2 Meeting		
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Teleconference: CMC, Request Status Update on Feb 14, 2006 Serial 503	31-Mar-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0528	31-Mar-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical and Statistical Comments Regarding Serial 457	03-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Study EGF100151 Serial No.: 0530	03-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Request for Type B Pre-NDA Meeting (Treatment of Relapsed, ErbB2-Advanced/Metastatic Breast Cancer) Serial No.: 0531	05-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0533	06-Apr-2006	No
GSK Telephone Conversation	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	07-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Clinical, Study Report (Protocol EGF10019) Serial No.: 0535	10-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0536	10-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document Scheduled May 16, 2006 Meeting Serial No.: 0532	10-Apr-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: CMC, Type A Meeting Request Serial No.: 0534	10-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0541	11-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0540	11-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0539	11-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0538	11-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation Serial No.: 0537	11-Apr-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Teleconference: CMC, Request Status Update of Feb 14, 2006 Serial 503	12-Apr-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: CMC; Responses to Questions Raised in Serial 503	13-Apr-2006	No
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: CMC	13-Apr-2006	No
GSK Correspondence	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) Serial No.: 0091 IND 69,184; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) - AMD Serial No.: 0024 IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Serial No.: 0542 1	18-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	19-Apr-2006	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Initial Serial No.: 0543		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Clinical, Investigator's Brochure Version 06 Serial No.: 0544	19-Apr-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the May 26, 2006 Type B, Pre-NDA Meeting	20-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Request for Type A Meeting; Treatment Protocol/Expanded Access to Lapatinib for Patients with Advanced/Metastatic Breast Cancer Serial No.: 0545	20-Apr-2006	No
FDA Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: CMC; Lapatinib Accepted into the FDA Quality Assessment Pilot Program	24-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0547	25-Apr-2006	No
GSK Correspondence	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) Serial No.: 0093 IND 69,184; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) - AMD Serial No.: 0025 IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Serial No.: 0546 1	25-Apr-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Withdrawal of Apr 10, 2006 Meeting Request	28-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document Preparation for May 26,2006 Pre-NDA Meeting Serial No.: 0548	28-Apr-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 003 to Protocol EGF103009 Serial No.: 0549	01-May-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0551	03-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0552	03-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0550	03-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0556	04-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0555	04-May-2006	No
GSK Correspondence	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) Serial No.: 0097 IND 69,184; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) - AMD Serial No.: 0028 IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Serial No.: 0554	04-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Request for FDA Guidance (Carcinogenicity Studies) Serial No.: 0553	04-May-2006	No
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Special Protocol Assessment - Not Appropriate: Clinical; FDA Responded to GSK's Mar 20, 2006 Request for a Special Protocol Assessment	05-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Type B Meeting Request: CMC Serial No.: 0557	05-May-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details for the May 31, 2006 Type A Meeting	08-May-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) Serial No.: 0098 IND 69,184; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) - AMD Serial No.: 0029 IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Serial No.: 0558 1	08-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0560	09-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0559	09-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0561	10-May-2006	No
GSK Trip Report	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Type: End of Phase II Meeting: Inflammatory Breast Cancer and Breast Cancer Brain Metastases	16-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Request for FDA Guidance for Protocol EGF103659 Serial No.: 0566	17-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0565	17-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0564	17-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Nonclinical, Study Reports Serial No.: 0563	17-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigators Serial No.: 0562	17-May-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) Serial No.: 0103 IND 69,184; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) - AMD Serial No.: 0031 IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Serial No.: 0567 1	19-May-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	22-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0572	24-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0571	24-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0570	24-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0569	24-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Request for Special Protocol Assessment: Mouse Carcinogenicity Protocol Serial No.: 0568	24-May-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: FDA Minutes of May 16 Meeting (IBC)	26-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0575	30-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0574	30-May-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0573	30-May-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: ASCO Presentations	31-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0578	31-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0577	31-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0576	31-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 07 to Protocol EGF100151 Serial No.: 0579	31-May-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document, CMC Meeting June 16, 2006 Serial No.: 0580	01-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0581	02-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF103659- Treatment Protocol, Informed Consent Form Serial No.: 0582	05-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol Protocol EGF30001, Amendment 6 Serial No.: 0584	07-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up	07-Jun-2006	No

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0583		
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Treatment Protocol EGF103659 is Acceptable	09-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendments 1 and 2 for EGF100262 Serial No.: 0586	12-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol Amendment 1 for EGF100161 Serial No.: 0585	12-Jun-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	13-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0588	15-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 0587	15-Jun-2006	No
GSK Trip Report	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Type: Pre-NDA CMC Meeting	16-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation Serial No.: 0589	19-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Request for Special Protocol Assessment: Carcinogenicity Serial No.: 0593	21-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0592	21-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0591	21-Jun-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0590	21-Jun-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment: Response to GSK Carcinogenicity Correspondence SN 0593	22-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0596	23-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0595	23-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0594	23-Jun-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details: GSK Attendees	27-Jun-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Special Protocol Assessment - Appropriate: Carcinogenicity	27-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0597	28-Jun-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol Protocol EGF105084 Amendment 003 Serial No.: 0598	05-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0601	10-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0600	10-Jul-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator, Other 1572 Change Serial No.: 0599	10-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0602	13-Jul-2006	No
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of Meeting: June 16, 2006 CMC Meeting	14-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0603	14-Jul-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: CMC; List of Commercial Manufacturers	17-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0608	19-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0607	19-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0606	19-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0605	19-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0604	19-Jul-2006	No
FDA Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: CMC; FDA Would Like Upcoming Additional Indications and Formulations to Go Through the Pilot Program	21-Jul-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0613	24-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0612	24-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0611	24-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0610	24-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0609	24-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0615	26-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF105485; New Investigator Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 0614	26-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF10011 Amendment 003 Serial No.: 0618	28-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF10003 Amendment 008 Serial No.: 0617	28-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF20014 Amendment 003	28-Jul-2006	No

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0616		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0622	31-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0620	31-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0619	31-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Meeting Request: Type A - Clinical Program for Treatment of Patients With Early Breast Cancer Following Completion of (Neo)adjuvant Chemotherapy Serial No.: 0621	31-Jul-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 01 to Protocol EGF104900 Serial No.: 0626	02-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0625	02-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0624	02-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0623	02-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 1 to Protocol EGF103659 Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 0627	03-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial	07-Aug-2006	No

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0630		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0629	07-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF103892; New Investigator Serial No.: 0628	07-Aug-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	08-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New and Revised Investigator Documentation Serial No.: 0631	09-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator, Other 1572 Change Serial No.: 0632	11-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0636	15-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0635	15-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0634	15-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0633	15-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0638	16-Aug-2006	No
GSK Telephone	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	16-Aug-2006	No

Communication Type	Re Line	Date	Attachments?
Conversation	7-Day Safety Report		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0637	16-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Meeting Request for Type B End of Phase 2 Meeting (Lapatinib in Combination with Letrozole in First Line Treatment for Metastatic Breast Cancer in Postmenopausal Women	17-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0640	22-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0643	23-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0642	23-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0641	23-Aug-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	25-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF104383 Amendment 1 Serial No.: 0645	29-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document (Tykerb for Early Breast Cancer following Completion of Adjuvant or Neo-Adjuvant Chemotherapy) Scheduled Sep 26, 2006 Meeting Serial No.: 0644	29-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	30-Aug-2006	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Initial Serial No.: 0652		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0651	30-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0650	30-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0649	30-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0648	30-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0647	30-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0646	30-Aug-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0654	01-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0653	01-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF105884, New Investigator Serial No.: 0655	05-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0658	08-Sep-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0657	08-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0656	08-Sep-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	11-Sep-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	11-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0662	13-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0661	13-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0660	13-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0659	13-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document Supplement to Aug 29, 2006 Briefing Document for Scheduled Sep 26, 2006 Type B End of Phase 2 Meeting Serial No.: 0663	14-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0666	18-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0665	18-Sep-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0664	18-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0667	18-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: Briefing Document, Clinical Scheduled Oct 30, 2006 EOPII Meeting - Lapatinib in the Initial Treatment of Postmenopausal Women with Hormone-Sensitive Metastatic Breast Can	22-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0671	25-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0670	25-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0669	25-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0674	28-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0673	28-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0672	28-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0676	29-Sep-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0675	29-Sep-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0677	04-Oct-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Provided Questions for Oct 30, 2006 Meeting	06-Oct-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Protocol: Study Design Resolution	06-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to Oct 2, 2006 FDA Request for a Publication Cited in the Sep 22, 2006 Briefing Document Serial No.: 0681	06-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF105485 Amendment 1 Serial No.: 0680	06-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0679	06-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0678	06-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0682	10-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0683	11-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0688	13-Oct-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0687	13-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0686	13-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Protocol EGF105884 Serial No.: 0685	13-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0684	13-Oct-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request: Clinical; FDA Provided Responses to GSK's Questions Related to the Aug 17, 2006 Meeting Request	16-Oct-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	16-Oct-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	20-Oct-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Proposed Protocol Amendment for EGF103659	24-Oct-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Revised Statistical Proposal for Adjuvant Study	24-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0693	24-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0692	24-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	24-Oct-2006	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Initial Serial No.: 0691		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0690	24-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0689	24-Oct-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	24-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0695	25-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0694	25-Oct-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: GSK Meeting Participants for the Oct 30, 2006 Meeting	26-Oct-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Statistical Information to Prepare for the Oct 30, 2006 Meeting	26-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence; Proposed Amendment to Protocol EGF103659 Serial No.: 0696	26-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0698	31-Oct-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0705	01-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up	01-Nov-2006	No

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0704		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0703	01-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0702	01-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0701	01-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0700	01-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0699	01-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF104334, Amendment 001 Serial No.: 0706	03-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF105884, Amendment 001 Serial No.: 0707	03-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence: - Response to FDA Questions (Tykerb for Early Breast Cancer Following Completion of Adjuvant or Neo-Adjuvant Chemotherapy) Serial No.: 0708	06-Nov-2006	No
FDA FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Comment/Information Request	07-Nov-2006	No
FDA Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Minutes of May 16, 2006 Meeting	07-Nov-2006	No

Communication Type	Re Line	Date	Attachments?
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Response to FDA Request/Comment: Proposed Amendment to EGF103659	07-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0709	08-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0713	13-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0712	13-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0711	13-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0710	13-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0718	14-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0717	14-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0716	14-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0715	14-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0714	14-Nov-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0724	15-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0723	15-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0722	15-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0721	15-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0720	15-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0719	15-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF103009 Amendment 4 Serial No.: 0727	17-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0726	17-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0725	17-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0730	20-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	20-Nov-2006	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Follow-up Serial No.: 0729		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator, Other 1572 Change Serial No.: 0728	20-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF103659 Amendment 2 Serial No.: 0731	21-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0735	27-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0734	27-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0733	27-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0732	27-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0737	30-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Correspondence - Request for FDA Guidance on IDMC Recommendation to Terminate Enrollment into Study EGF100151 Serial No.: 0736	30-Nov-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0739	04-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial	04-Dec-2006	No

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0738		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0743	05-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0742	05-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0741	05-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0740	05-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol, Clinical Protocol Amendment: New Investigator, Investigator Add Protocol EGF102988 Serial No.: 0744	06-Dec-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	11-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0745	12-Dec-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details: GSK Participants in Oct 30, 2006 Meeting	13-Dec-2006	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum: Meeting Agenda or Details: More Details on GSK Participants in Oct 30, 2006 Meeting	14-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0753	14-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	14-Dec-2006	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Initial Serial No.: 0752		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0751	14-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0750	14-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0749	14-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0748	14-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0747	14-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0746	14-Dec-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	15-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF10061Amendment 2 Serial No.: 0754	15-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0755	18-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0761	19-Dec-2006	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0760	19-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0759	19-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0758	19-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0757	19-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0756	19-Dec-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	20-Dec-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	21-Dec-2006	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	22-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0765	22-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0764	22-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0763	22-Dec-2006	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	22-Dec-2006	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Follow-up Serial No.: 0762		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0767	02-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0766	02-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Treatment Protocol: Clinical Serial No.: 0768	03-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0775	04-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0774	04-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0773	04-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0772	04-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0771	04-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0770	04-Jan-2007	No
GSK Correspondence	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) Serial No.: 0222 IND 69,184; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) - AMD	04-Jan-2007	No

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0117 IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Serial No.: 0769 1		
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	04-Jan-2007	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	05-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0778	05-Jan-2007	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	05-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0777	05-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0776	05-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF104334 Amendment 002 Serial No.: 0779	08-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0780	09-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0781	09-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0782	12-Jan-2007	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0786	15-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0785	15-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0784	15-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0783	15-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0795	17-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0794	17-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0793	17-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0792	17-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0791	17-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0790	17-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial	17-Jan-2007	No

Communication Type	Re Line	Date	Attachments?
	Serial No.: 0789		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0788	17-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0787	17-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0796	22-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0801	24-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0800	24-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0799	24-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0798	24-Jan-2007	No
GSK Correspondence	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) Serial No.: 0236 IND 69,184; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) - AMD Serial No.: 0128 IND 76,899; Pazopanib Eyedrops (GW786034 - VEGFR tyrosine kinase inhibitor) - A	24-Jan-2007	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	29-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0805	31-Jan-2007	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0804	31-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0802	31-Jan-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0803	31-Jan-2007	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	01-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0813	02-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0812	02-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0811	02-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0810	02-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0809	02-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0808	02-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0807	02-Feb-2007	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0806	02-Feb-2007	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	05-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0823	05-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0822	05-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0821	05-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0820	05-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0819	05-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0818	05-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0817	05-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0816	05-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0815	05-Feb-2007	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0814	05-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator Serial No.: 0825	06-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Investigator, Investigator Add Serial No.: 0824	06-Feb-2007	No
GSK Correspondence	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) Serial No.: 0251 IND 69,184; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) - AMD Serial No.: 0140 IND 76,899; Pazopanib Eyedrops (GW786034 - VEGFR tyrosine kinase inhibitor) - A	07-Feb-2007	No
GSK Correspondence	IND 65,747; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) Serial No.: 0250 IND 69,184; pazopanib (GW786034 - VEGF Tyrosine Kinase Inhibitor) - AMD Serial No.: 0139 IND 76,899; Pazopanib Eyedrops (GW786034 - VEGFR tyrosine kinase inhibitor) - A	07-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Amendment 4 for EGF105084 Serial No.: 0829	08-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol; Amendment 2 to EGF105485 Serial No.: 0828	08-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0833	13-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0832	13-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	13-Feb-2007	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Follow-up Serial No.: 0831		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0830	13-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0841	14-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0840	14-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0839	14-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0838	14-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0837	14-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0836	14-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0835	14-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0834	14-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0848	20-Feb-2007	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0847	20-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0846	20-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0845	20-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0844	20-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0843	20-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0842	20-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization (Cross Reference Letter - Dr. Le) Serial No.: 0852	21-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0851	21-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0850	21-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol 103890 Protocol Amendment: Change in Protocol; Amendment 001 to Protocol 103890 Serial No.: 0853	21-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	21-Feb-2007	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Follow-up Serial No.: 0849		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0854	22-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0860	26-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0859	26-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0858	26-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0857	26-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0856	26-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0855	26-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization Serial No.: 0861	27-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0865	28-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0864	28-Feb-2007	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0863	28-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0862	28-Feb-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol EGF108916, Clinical Serial No.: 0866	01-Mar-2007	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol LPT109096, Clinical Serial No.: 0867	01-Mar-2007	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: New Protocol LPT108741, Clinical Serial No.: 0868	01-Mar-2007	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	02-Mar-2007	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	02-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Annual Report Period Covering Dec 6, 2005 through Dec 5, 2006 Serial No.: 0869	02-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0874	05-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0873	05-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0872	05-Mar-2007	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0871	05-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0870	05-Mar-2007	No
GSK FAX/E-mail	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor General Memorandum	07-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Change in Protocol, Clinical Protocol EGF104383 Serial No.: 0875	07-Mar-2007	Yes
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0877	09-Mar-2007	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	09-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Amendment: Other, Letter of Authorization for Dr. Saul Rivkin Serial No.: 0876	09-Mar-2007	Yes
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	12-Mar-2007	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0888	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0887	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor	13-Mar-2007	No

Communication Type	Re Line	Date	Attachments?
	15-Day ADR Report: Follow-up Serial No.: 0886		
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0885	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0884	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0883	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0882	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0881	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0880	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0879	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0878	13-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0891	14-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Follow-up Serial No.: 0890	14-Mar-2007	No

Communication Type	Re Line	Date	Attachments?
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 15-Day ADR Report: Initial Serial No.: 0889	14-Mar-2007	No
GSK Telephone Conversation	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor 7-Day Safety Report	15-Mar-2007	No
GSK Correspondence	IND 61,362; Lapatinib (GW572016) Tyrosine Kinase Inhibitor Protocol Amendment: Protocol EGF102988 New Investigator; Investigator Revision Serial No.:0893	15-Mar-2007	Yes

EXHIBIT 9B

NDA diligence log

Regulatory Affairs
CARDS
View Manager Brief Report

Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb™ (lapatinib ditosylate)Tablets Original Submission	25-Aug-2006	No
GSK Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Teleconference: Submission of CMC Section and Discussion of Prior Approval Inspection	07-Sep-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Original Submission - Completion of NDA with Quality Section Submission User Fee: With Clinical Data	13-Sep-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Correspondence: CMC Field Copy	13-Sep-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical Response to FDA Questions of Sep 10, 2006	15-Sep-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: CMC; Confirmation of Registration Numbers for Manufacturing Sites	20-Sep-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: FDA Requested a Word Version of the Drug Substance and Drug Product cQOS Submitted in Module 2	20-Sep-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: CMC; Confirmation of Registration Numbers for Manufacturing Sites	20-Sep-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets	22-Sep-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
		Response to FDA Request/Comment: CMC		
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Amendment to Pending Application: Clinical Updated Clinical Study Report for EGF100151 .	04-Oct-2006	No
GSK Trip Report		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets NDA Presentation Prior to Day 45 Meeting	10-Oct-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Proposal for the 120-Day Safety Update	11-Oct-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Correspondence; Proposal for 120 Day Safety Update	11-Oct-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request for Data and Datasets to Support the QT Analyses for Study EGF10003	17-Oct-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Response to GSK's Clarification Request and an FDA Request for Clarification Regarding the May 26, 2006 Pre-NDA Meeting	17-Oct-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Access to Perceptives Imaging Equipment	17-Oct-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clarification Requested on FDA's	17-Oct-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
		Question Regarding HER2 Overexpression at the 45-Day Meeting		
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Meeting Agenda or Details Regarding the May 26, 2006 Pre-NDA Meeting	18-Oct-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: May 26, 2006 Pre-NDA Meeting and HER2 Overexpression	18-Oct-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: QT Analysis for EGF10003	19-Oct-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA's Oct 17, 2006 Biopharm Request	23-Oct-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Other Booklet from Oct 5, 2006 Meeting	23-Oct-2006	No
FDA Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: CMC	25-Oct-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: CMC; Oct 25, 2006 Information Request Letter	25-Oct-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical Clarification Regarding Datasets for Protocol EGF100151	26-Oct-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	30-Oct-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Draft Labeling in Response to Oct 25, 2006 Request	30-Oct-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Clinical; Determining Randomization Assignment Versus Treatment Received	31-Oct-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Supplement Request: PLR Labeling	31-Oct-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical Protocol EGF10003 NONMEM Datasets	31-Oct-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical Additional Biopharmacology Information in Response to Oct 31, 2006 Request	02-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: FDA Notice of Planned Launch Advertising	06-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical	08-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets	08-Nov-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
		Response to FDA Request/Comment: Clinical		
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Clinical, Statistical Question for EGF100151	08-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical Questions Regarding EGF100151	09-Nov-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request	09-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment	09-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical Response to Nov 6, 2006 Request Regarding Protocol EGF100151	09-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Correspondence: CMC Field Copy	10-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Amendment to Pending Application: CMC Addition of Zebulon for Secondary Packaging and Labeling	10-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical Response to Nov 8, 2006 Request from ClinPharm Reviewers	10-Nov-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical Response to Nov 8, 2006 Email Request	10-Nov-2006	No
FDA Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Acknowledgement: NDA # Assigned	13-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical Information for EGF100151	13-Nov-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Clinical	13-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets 120-Day Safety Update: Safety	15-Nov-2006	No
GSK Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Teleconference: CMC, Labeling	16-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical: % Treated Days During Treatment Period Using Two Methods of Calculation	16-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Use of Established Name	17-Nov-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets	17-Nov-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
		Comment/Information Request: CMC; Impurities in Drug Substance		
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Correspondence: CMC Field Copy	17-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Amendment to Pending Application: CMC	17-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Nonclinical; Certificates of Analysis for the 6-Month Rat and 9-Month Dog Studies	17-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Nonclinical Certificates of Analysis	17-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: BA/BE, Clinical Response to Nov 14, 2006 Request for Calculation of "% Treated Days During Treatment Period"	17-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Correspondence: Advertising/Promotion Request for Advisory Comment	17-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Nonclinical: Tykerb Impurity Justification	20-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Nonclinical; Corrected Impurity Justification and Certificates of Analysis	21-Nov-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: CMC, Nonclinical Correction to Impurity Content in Table Submitted Nov 17, 2006 and Certificate of Analysis	21-Nov-2006	Yes
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Advertising/Promotion, CMC, Labeling Requested Change to USAN Established Name	21-Nov-2006	Yes
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Use of Established Name	22-Nov-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Statistical Query	22-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Statistical	22-Nov-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Statistical Query	22-Nov-2006	No
FDA Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Labeling; Identification of Potential Review Issues for the Sep 15, 2006 Submission	24-Nov-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Labeling	27-Nov-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets	27-Nov-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
		Comment/Information Request: Clinical, Statistical		
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Bottle Label	27-Nov-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request for the Originally Submitted Proposed Bottle Label	27-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request for Certificates of Analysis for Preclinical Studies	27-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Statistical	27-Nov-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical	28-Nov-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comments Following Up from the Nov 16, 2006 Teleconference	29-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Nonclinical, Statistical Response to Nov 27, 2006 Email Request	30-Nov-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Correspondence: CMC Field Copy	01-Dec-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Amendment to Pending Application: CMC, Labeling	01-Dec-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Revised Tykerb Bottle Label	05-Dec-2006	No
FDA Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets CMC: Quality by Design Review Comments/Requests	06-Dec-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: CMC	06-Dec-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Clinical Pharmacology Question Regarding HER2 Overexpression	08-Dec-2006	No
FDA Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: CMC	08-Dec-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical Response to Dec 4, 2006 "Clinpharm group" Question Regarding HER2 Testing	08-Dec-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	13-Dec-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Correspondence: CMC Field Copy	13-Dec-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Amendment to Pending Application: CMC	13-Dec-2006	No
FDA Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Advertising/Promotion: Planned Launch Advertising	14-Dec-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Determination of Randomization Assignment Versus Treatment	15-Dec-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Meeting Agenda or Details for Dec 18, 2006 Teleconference	18-Dec-2006	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical; HER2 Testing on EGF100151	18-Dec-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Correspondence: CMC Field Copy	18-Dec-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Amendment to Pending Application: CMC	18-Dec-2006	No
FDA Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Teleconference: Minutes from Dec 20, 2006 Teleconference Comment/Information Request: Clinical, Labeling, Statistical	20-Dec-2006	No
FDA Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: CMC: Methods Validation on Lapatinib Ditosylate Tablets, 250 mg	20-Dec-2006	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: BA/BE, Clinical Response to Dec 15 and Dec 22, 2006 Requests Regarding Protocol EGF100151	22-Dec-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical Detailed Information on Four Subjects	22-Dec-2006	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Clinical	22-Dec-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical	22-Dec-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical (QR) Response to NDA with Clarifications based on Dec 20, 2006 Telecon	22-Dec-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical (AI)	22-Dec-2006	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	09-Jan-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical	09-Jan-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical Dataset for Protocol EGF100151 Patients Who Progressed	09-Jan-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical; Documented Erb B Overexpression Information for EGF100151	10-Jan-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Efficacy, Statistical	11-Jan-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical; Expanded Access Program	17-Jan-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment; Investigator Checklist	17-Jan-2007	No
GSK Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Teleconference; Status of Review	17-Jan-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical Response to Jan 17, 2007 Request for Patient CRFs	18-Jan-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: BA/BE, Clinical Protocol EGF100151 - Patient HER2 Testing	18-Jan-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets	19-Jan-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
		Response to FDA's Jan 17, 2006 Statistical Questions		
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA's Jan 17, 2007 Email Request: Case Report Forms for Specific Patients	19-Jan-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Statistical Response to Jan 17, 2007 Request Regarding Protocol EGF100151	19-Jan-2007	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Statistical	23-Jan-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Receipt of Email Request and Request for a Teleconference	23-Jan-2007	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Status Update to Statisticians	23-Jan-2007	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: GSK Question from Jan 17, 2007 Email	23-Jan-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Statistical Response to Jan 23, 2007 Statistician Request	24-Jan-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Resubmission: Clinical Resubmission of Jan 18, 2007 Submission	24-Jan-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
FDA Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Teleconference; Clinical Statistical Discussion of how best to characterize the treatment effect relative to labeling	25-Jan-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib)Tablets Response to FDA Request/Comment: Clinical, Labeling, Statistical Draft Labeling - Inclusion of Apr 2006 Analysis of Protocol EGF100151	29-Jan-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: GSK Attendees in the Jan 25, 2007 Teleconference	29-Jan-2007	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Labeling	01-Feb-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Amendment to Pending Application: Patent Information	01-Feb-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	02-Feb-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum	02-Feb-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Labeling	06-Feb-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets	06-Feb-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
		Response to FDA Request/Comment: Labeling Revised Labeling in PLR Format		
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Amendment to Pending Application: Patent Information Replacement for Feb 1, 2007 Submission with Typographical Errors	06-Feb-2007	No
FDA Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Acknowledgement: Receipt of Sample Materials and Equipment	15-Feb-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	19-Feb-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Correspondence: Clinical, Nonclinical, Phase IV Commitment Proposed Postmarketing Commitments	26-Feb-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	28-Feb-2007	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Labeling	28-Feb-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	01-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	01-Mar-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
		Response to Dec 6, 2006 Correspondence Regarding Bottle Labels		
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Labeling, Meeting Request	05-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	05-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Revised bottle label for Tykerb	05-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Response to Mar 2, 2007 Revisions to Draft Labeling	05-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Labeling, Meeting Agenda or Details	05-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	05-Mar-2007	No
FDA Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Teleconference: Other; Clinical, Labeling GSK Minutes from the March 6, 2007 FDA Teleconference on Tykerb Prescribing Information	06-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling, Protocol	06-Mar-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
		Provided Protocols EGF10015 (Midazolam) and EGF10009 (Paclitaxel) Amendment 3		
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Labeling	06-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	06-Mar-2007	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Labeling, Phase IV Commitment, Safety	06-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Labeling, Meeting Agenda or Details Provided a list of GSK participants from the March 6, 2007 teleconference	06-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	06-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	06-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Revised Labeling	06-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	06-Mar-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Revised Bottle Label	06-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Safety Provided Safety Report for B0429733A	07-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Safety, Protocol Provided signed File Note on patient 00110	07-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Safety	07-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Advertising/Promotion	07-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling, Safety Provided Safety Report B0429733A for Protocol EGF100151	07-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib)Tablets Response to FDA Request/Comment: Labeling Narrative on Patient with LVEF	07-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib)Tablets Response to FDA Request/Comment: Labeling Revised Bottle Label	07-Mar-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Phase IV Commitment Proposed Post Marketing Commitments	07-Mar-2007	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Labeling	08-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	08-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Provided receipts for electronic submissions to NDA	08-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Labeling, Meeting Agenda or Details	08-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Provided Receipts for Electronic Submissions to NDA	08-Mar-2007	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Labeling	08-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment	08-Mar-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling, Safety Provided File Note on Patient #00110 (B0429733A)	08-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Suggested Revisions to Prescribing Information	08-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	08-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Additional Information on Patient with LVEF	08-Mar-2007	No
FDA Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Teleconference: Other, Labeling, Safety, Post Marketing Commitment GSK Minutes from the March 9, 2007 FDA Teleconference on Tykerb Prescribing Information	09-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling PI with DSRCS Comments/FDA Edits	09-Mar-2007	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Labeling PI with DSRCS Comments/FDA Edits	09-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Other FDA Tykerb Burst	12-Mar-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
FDA Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Teleconference: Other, Labeling, Clinical, Statistics GSK Minutes from the March 12, 2007 FDA Teleconference on Tykerb Prescribing Information	12-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Clinical, Efficacy, Labeling, Protocol Proposed/Clean PI for Tykerb	12-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	12-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment List of GSK Participants from the March 9, 2007 Teleconference	12-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	12-Mar-2007	No
FDA Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Approval Letter: Labeling, Phase IV Commitment	13-Mar-2007	No
GSK Telephone Conversation		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Teleconference: CMC Tykerb Shelf Life	13-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: CMC, Labeling Tykerb Approval Letter - Shelf Life	13-Mar-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment Email of the Tykerb Approval Letter	13-Mar-2007	No
FDA FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Comment/Information Request: Labeling	13-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	13-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	13-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	13-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling	13-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Revised Bottle Label	13-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment: Labeling Revised PI - Clean and Marked Up Versions	13-Mar-2007	No

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Communication Type	Seq No	Re Line	Date	Attachments?
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: CMC Tykerb Shelf Life	14-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	14-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	14-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	14-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Correspondence	14-Mar-2007	Yes
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: Advertising/Promotion Word Version of the GSK Press Release for Tykerb	15-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets General Memorandum: CMC	15-Mar-2007	No
GSK FAX/E-mail		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to FDA Request/Comment	15-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	16-Mar-2007	No

Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	16-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	16-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	19-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	20-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	20-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	21-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials	21-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	22-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Supplement: Changes Being Effected, Labeling	22-Mar-2007	No

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Communication Type	Seq No	Re Line	Date	Attachments?
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Response to Approval Letter: FPL	22-Mar-2007	No
GSK Correspondence		NDA 22-059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	23-Mar-2007	No
GSK Correspondence		015-Day ADR Report	26-Mar-2007	No
GSK Correspondence		NDA 022059; Tykerb® (lapatinib ditosylate)Tablets Transmittal of Advertisements and Promotional Materials: Advertising/Promotion	28-Mar-2007	No
GSK Correspondence		NDA 021077; ADVAIR DISKUS® (fluticasone propionate/salmeterol inhalation powder) 100/50 mcg, 250/50 mcg and 500/50 mcg NDA 014691; ALKERAN® (melphalan) Tablets NDA 050461; ANCEF® (cefazolin for injection) NDA 021345; Arixtra® (fondaparinux sodium) NDA	30-Mar-2007	No

EXHIBIT 10

Patent Term Extension Calculations

Patent Term Extension Calculation for U.S. Patent No. 6,713,485

Patent Issue Date: March 30, 2004

IND Effective Date: January 5, 2001

NDA Submission Date: September 13, 2006

NDA Approval Date: March 13, 2007

IND 61,632 Regulatory Review Period Occurring After Date of Patent Issuance

3/31/2004-9/12/2006

3/31/2004	=	1
4/1/2004- 4/30/2004	=	30
5/1/2004-5/31/2004	=	31
6/1/2004- 6/30/2004	=	30
7/1/2004- 7/31/2004	=	31
8/1/2004- 8/31/2004	=	31
9/1/2004- 9/30/2004	=	30
10/1/2004- 10/31/2004	=	31
11/1/2004-11/30/2004	=	30
12/1/2004-12/31/2004	=	31
1/1/12005-12/31/2005	=	365
1/1/2006-1/31/2006	=	31
2/1/2006-2/28/2006	=	28
3/1/2006-3/31/2006	=	31
4/1/2006-4/30/2006	=	30
5/1/2006-5/31/2006	=	31
6/1/2006-6/30/2006	=	30
7/1/2006-7/31/2006	=	31
8/1/2006-8/30/2006	=	30
9/1/2006-9/12/2006	=	11
		895 days

Testing Phase

IND Phase / 2 = 895 / 2 = **447.5 days**

NDA 22-059 Regulatory Review Period

9/13/2006-3/13/2007

9/13/2006-9/30/2006=	18
10/1/2006-10/31/2006=	31
11/1/2006-11/30/2006=	30
12/1/2006-12/31/2006=	31
1/1/2007-1/31/2007=	31
2/1/2007-2/28/2007=	28
3/1/2007-3/13/2007=	12
	181 days

IND phase/2 + NDA phase =447+181 = 628

Total Patent Term Extension: 628 days

5 year Patent Term Extension (35 U.S.C. § 156(g)(6)(A)) Cap does not apply.

14 years from NDA approval date: 3/13/2007 + 14 years = 3/13/2021

Expiry with Extension: 1/8/2019 + 628 days = 9/27/2020